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TWENTIETH CENTURY

PRACTICE

AN INTERNATIONAL ENCYCLOPEDIA

OF

MODERN MEDICAL SCIENCE

BY

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EDITED BY

THOMAS L. STEDMAN, M.D.

NEW YORK CITY

IN TWENTY VOLUMES

VOLUME VII

DISEASES OF THE RESPIRATORY ORGANS AND BLOOD, AND FUNCTIONAL SEXUAL DISORDERS

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DISEASES OF THE PLEURA.

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DISEASES OF THE PLEURA.

PLEURISY.

The classification of pleural inflammations adopted in the following pages needs no apology. A purely etiological division of the subject is still impossible, great as the progress of the past few years in this direction has been. Distinctions based upon acuteness and chronicity are hardly applicable to an affection like pleurisy, in which there are innumerable gradations between the two extremes. The character of the exudate, whether fibrinous, serofibrinous, or purulent, still remains the prominent factor which regulates both the prognosis of the disease and its practical management by the physician.

Dry Pleurisy.

Definition.—Dry or fibrinous pleurisy is an acute or chronic inflammation of the whole or a part of the pleural membrane, characterized by an exudation of fibrin upon the free surface of the latter.

Etiology.

Dry pleurisy is a very common disease. This is to be inferred not so much from its clinical frequency as from the fact that in autopsies it is almost an exceptional occurrence to find the pleura entirely free from adhesions. Smith, for example, in a series of one hundred and twenty post-mortem examinations in individuals who had died from all sorts of diseases, found adhesions in no less than eighty per cent. That such adhesions are extremely frequent is certainly in accord with the general experience of most observers.

As a primary affection, however, dry pleurisy is comparatively rare; Engster, among one hunded and sixty-three cases of apparently primary pleurisy, found only sixteen of the dry form.

Three possible causes of primary dry pleurisy are commonly given, viz., cold, rheumatism, and tuberculosis. The latter form of primary dry pleurisy, that is to say, a primary pleural tuberculosis which, from beginning to end, produces a purely fibrinous exudate,

is extremely rare. A dry pleurisy as a local expression of the rheumatic diathesis is possibly more common; Peter, at all events, is of this opinion, though it is probable that the serofibrinous form of rheumatic pleurisy is far more frequent. Finally, the influence of cold would seem to be unquestionable in such instances, for example, as those cited by Fraentzel in his article in Ziemssen's Cyclopædia; and yet one cannot help thinking that here, as elsewhere, exposure in its various forms can play at best but a subordinate rôle—the prologue to some form of bacterial infection.

Most fibrinous pleurisies are secondary, and their great anatomical frequency is to be ascribed chiefly to the fact that nearly all acute affections of the lung are accompanied by a fibrinous inflammation of the adjoining pleura; so with all forms of pneumonia, with abscesses, and with infarctions. Less often the infection comes from without, and must be sought in affections of the axillary glands or of the breast, or it follows trauma, with or without a perforating wound; especially cancer of the breast is not infrequently complicated by a dry pleurisy. Rarely the channel of infection may be through the diaphragm—as so often occurs with inflammatory affections of the liver.

But the disease upon which particular emphasis is to be laid in the etiology of dry pleurisy is pulmonary phthisis. Few cases of the latter, possibly none, run their course without sooner or later developing a dry pleurisy. It is one of the commonest of the many complications which vary the clinical course of phthisis. Smith, in one hundred and forty cases of pleural adhesions, found pulmonary phthisis in over thirty-three per cent., and cheesy nodules in the lungs in a large number of the remaining; in only nine cases, however, did the pleuræ contain tubercles, and it is probable that but a very small proportion of the dry pleurisies which complicate pulmonary phthisis are themselves tuberculous.

Pathological Anatomy.

It is seldom that an opportunity is presented for observing the early pathological appearances of dry pleurisy. Judging, however, from analogy, and from observation of the pleuræ of dogs after the injection of irritating substances, the succession of anatomical changes is probably the following: First, the affected portion of the pleura is seen to be slightly reddened, although its glistening appearance is not immediately lost; rarely the whole costal and pulmonary pleura may be thus involved; but in by far the greater proportion of cases the affected region is comparatively limited. This

initial redness grows more intense until, after the lapse of a few hours, the next stage in the inflammatory process begins—that of exudation. The membrane now begins to lose its gloss and to look dull and opaque. On careful inspection a very thin coating of fibrin may then be perceived as a finely granular layer which is unevenly distributed over the inflamed surface. This fibrinous exudation rapidly increases and soon becomes plainly perceptible as a more or less shaggy membrane, the free surface of which presents a varying appearance of villi, knobs, and granules, or furrows. If, as is very often the case, the opposite pleural surface is likewise involved, the two become temporarily agglutinated, and connecting bands of fibrin pass from one surface to the other. If the membrane be scraped off the underlying pleura will be found apparently but little altered.

While these gross changes are taking place upon the surface, important histological processes are going on in the substance of the pleura itself, and in the deeper layers of the newly formed false membrane. At first the superficial vessels become engorged with blood, the lymph channels are distended, a few of the endothelial cells have fallen off in patches, and already, within the first six hours, a fine reticulum of fibrin may be perceived between and overlapping the endothelial cells. The superficial connective-tissue cells are also swollen and increased in number—changes which are often fully developed at the end of twenty-four hours (Delafield and Prudden). By the third or fourth day these cells, together with mononuclear leucocytes, have penetrated into the deeper layers of the false membrane, and at about the same time newly formed vessels appear upon the free surface of the pleura as small linear sprouts which project into the fibrinous layer above.

The subsequent development of this inflammatory process varies greatly with its intensity and duration, and also according to the frequency of its repetition. In some cases the ultimate residue of the process is very slight; the fibrinous exudate is wholly absorbed, the connective-tissue proliferation is insignificant, and there remains only a permanent white glistening spot of pleural thickening. In most cases, however, the quantity of newly formed tissue is more abundant. The proliferative process involves not only the surface of the pleura, but also the connecting bridles of fibrin between the opposite pleural walls; and later these become organized into adhesions which permanently unite the costal and pulmonary pleuræ, and considerably impair the respiratory mobility of the lung. As a result of successive attacks of dry pleurisy these adhesions may in time obliterate a large part or even the whole of both pleural cavities.

But the development of even a complete synechia of the pleural surfaces does not by any means exhaust the possible consequences of simple dry pleurisy. In a small proportion of cases, because either of unusual severity of the inflammatory process or of frequent and long-repeated attacks, the proliferation of pleural tissue may be excessive. It is unquestionably true that these cases of enormously thickened pleuræ are very apt to be tuberculous, and also that they are much more frequent as results of serofibrinous pleurisies than of the dry form. But they do assuredly follow the latter in some instances, and Sir Andrew Clark called especial attention to the relative frequency of this event, and to the serious train of consequences involved. Here the pleura may be found enormously thickened throughout—in extreme cases to an inch or even more. Furthermore, it appears to be rare for this process to be confined to the pleura alone. Ziegler states that even in an ordinary acute pleurisy it is not very exceptional for a lymphangitis to extend from the inflamed pleura along the lymphatics of the interlobular septa and possibly also to give rise to an interlobular pneumonia. In chronic pleural thickening this tendency to invasion of the lung by the proliferative process is still greater. The interlobular septa become also gradually thickened, first at the periphery, and then in the deeper parts of the lung, until finally the perivascular and peribronchial connective tissue becomes more or less universally involved. With this fibroid process there is a corresponding compression of the alveoli, which in part become atelectatic; also a development of bronchiectatic cavities from traction of the fibrous tissue and increased atmospheric pressure within. Eventually marked shrinking occurs which in time results in great deformity of the chest. The spine shows a lateral curvature, the shoulder droops, the scapula projects outwards, and the whole affected side of the thorax appears shrunken and depressed; the heart and mediastinum are drawn towards the affected side, and finally there is a development of circulatory and systemic changes which seriously jeopardize the life of the individual.

Symptoms.

These vary exceedingly according as the attack is primary or secondary, acute or chronic, of violent or of insidious onset.

An acute attack of primary dry pleurisy is usually attended by considerable constitutional disturbance and more or less pronounced respiratory symptoms. There is rarely any premonitory period, and the first and most prominent symptom is a severe pain in the side. This pain is usually described as sharp, cutting, or lancinating in

character. As a rule of only moderate severity and easily endured, it at times reaches a degree of violence which may well give it a high rank among the possible causes of intense suffering. Thus I have occasionally seen cases of acute pleuritic pain which even the largest doses of morphine seemed powerless to relieve; and in which the facial expression, the cries and contortions of the patient recalled vividly the agony of a biliary or renal calculus. But in the great majority of cases the pain is only moderate. It is felt oftenest, without doubt, at the seat of inflammation; and since this is usually in the lower and lateral regions of the pleura, owing probably to the greater mobility and consequent susceptibility of these parts, it is here also that the pain is usually felt—either just outside the nipple, or in the axillary region, or behind, near the angle of the scapula. In exceptional instances it is referred to the terminations of the intercostal nerves, and may then be located a considerable distance from the seat of inflammation—often lower down or farther forward. Very rarely it has been found at the umbilicus, thus suggesting a grave abdominal affection, or even upon the side opposite to the one diseased.

The pain of pleurisy is greatly aggravated by anything which increases the respiratory movement of the inflamed surfaces. The sufferer usually tries to avoid this by posture; but since local pressure is equally painful this attempt is often fruitless. Perhaps the majority of pleuritics lie upon the unaffected side, fearing the pressure of body weight more than the increased respiratory movement. Others lie upon the affected side; assuming, however, a semirotated position, so that while the respiratory excursions are restrained there is no direct pressure upon the region involved. Nothing aggravates the pain of acute pleurisy more than cough; hence the cough which usually attends the onset of the disease has a somewhat peculiar character; it is short, superficial, suppressed; forcibly held back, as it were, by the patient. This cough is rarely entirely lacking during the first few days of a dry pleurisy. It is dry, or at most attended by only the slightest expectoration of bronchial mucus. Its cause is doubtful. A direct pleural origin had always been assumed until Nothnagel claimed that artificial irritation of the pleura was powerless to provoke a cough, and ascribed that in question to an accompanying bronchitis; but Nothnagel's experiments have not been confirmed, and the matter still remains undecided. The cough of pleurisy usually persists until the inflammatory process either has subsided or has gone on to an abundant fluid exudation. The pain also, after remaining at its acme during perhaps the first two or three days, gradually disappears even in cases

in which a loud and constant friction still indicates the continuance of inflammation.

Another very common symptom of acute dry pleurisy is dyspnœa; this is not excessive as in pneumonia, but there is a variable increase in the rapidity of respiration according to the amount of pain. By a more shallow, and therefore of necessity more rapid respiration, the movement of the inflamed surfaces is reduced to a minimum, and the pain is made less violent.

The *constitutional symptoms* of the affection are of only moderate intensity. A chill is rare. The temperature rises at once to 102° or 103° F., remains there for two to three days, and then rapidly falls to normal. There are, of course, many variations from this type, but the symptoms hitherto described represent the usual course of acute idiopathic dry pleurisy.

But it can hardly be questioned that many primary pleurisies, possibly even a majority, are not known of or detected during life. Purely secondary forms will hardly account for the enormous frequency of pleuritic adhesions as disclosed upon the post-mortem table. We can only infer that in very many cases a primary pleurisy may develop insidiously and painlessly, and run its course to the production of newly formed tissue with none of the usual accompaniments of an acute inflammatory process. This would also further appear from the well-known clinical fact that a condition of enormous thickening of the pleura, with secondary involvement of the pulmonary septa and subsequent fibroid contraction, may develop almost without pain and unknown to the victim. Again, it is a matter of everyday occurrence, especially in pulmonary phthisis in which the attention is constantly called to the chest, to find well-marked friction, although neither pain nor any other respiratory or constitutional disturbance has suggested pleurisy. It is, therefore, to be regarded as comparatively frequent for a dry pleurisy to pursue throughout an absolutely latent and unrecognized course, which may exceptionally result in an important series of changes in the pleura and adjacent lung. The clinical bearing of these conditions will be more fully considered under the heading of pleural adhesions.

As to the symptomatology of secondary dry pleurisies, such as complicate the various pulmonary inflammations, notably croupous pneumonia and phthisis, little need be said. The affection is then but a more or less trivial incident in the course of the primary disease, and its symptoms are often wholly merged in those of the latter. In pneumonia it is probable that much of the acute pain is due to the complicating pleurisy; and in phthisis, when the pleural inflammation is less acute and widespread, its presence may be

suggested by rather transitory and fleeting pains about the shoulder and scapula, or, as stated, it may give rise to no rational signs whatever.

Physical Signs.

Practically the only physical sign of acute dry pleurisy is friction. Percussion is unchanged; and a diminished respiratory murmur, which might theoretically be presumed from the shallowness of respiration, has little or no clinical existence. Friction, however, more than compensates for the paucity of other signs because of its great constancy and its pathognomonic character. When heard, it is conclusive evidence of pleurisy, though pleurisy may undoubtedly exist without friction. As a rule, friction is one of the most easily recognizable and most distinctive of all the sounds which originate in the thorax. Once heard, it is ever afterwards unmistakable. Its rough, grating character is precisely what would be expected from the friction of two moist and roughened surfaces. Usually it accompanies both inspiration and expiration, beginning with the end of the former, and occupying nearly the whole of the latter. A deep inspiration may at times be necessary to its production. Its character is usually jerky; it is made up of separate rubs which give the impression as if one pleural surface moved over the other by a rapid succession of hitches. Sometimes its quality is creaking like that of new leather; again it resembles very closely the crumpling sound made in walking over newly fallen snow. These are the more common varieties. More rarely the sound is not so characteristic; it may be dryer and shorter, and is said in some instances to resemble a sonorous râle: such cases must be extremely rare. So also with the pleural "rustlings" described by certain authors as incident to the presence of chronic and extensive pleural thickening, and as somewhat similar to a subcrepitant râle; such sounds are occasionally heard, but whether they are of pleural or pulmonary origin is very difficult to decide.

Besides their peculiar quality, friction sounds have certain other characteristics which differentiate them more or less completely from pulmonary and bronchial râles. In the first place they are superficial and give this impression to the ear. Often they impart a fremitus to the hand laid upon the chest; and sometimes indeed the rub can be heard by the patient himself. Again, a friction sound is, as a rule, quite uninfluenced by cough; cough does not cause it in any way to change its quality or location as is often true of bronchial râles. A friction sound is local, at least it has a point of greatest intensity from which it is not widely transmitted; a

sonorous râle is often heard throughout the whole chest. But after all, these distinctions are of but little service; one instantly recognizes a rub simply because he has heard the same sound before.

The seat of friction in the great majority of cases is over the lower half of the chest, particularly in the region of the nipple in front, and of the angle of the scapula behind; it may be heard over the upper front, but any practitioner of experience will probably be surprised at the few cases he can recall in which the rub was heard above the third or fourth rib. And yet pleurisy as proven by adhesions is common enough over the upper lobes; it is probable that a certain amount of expansion is necessary to effect the necessary separation of the agglutinated pleural surfaces, and that this is only possible below, where the respiratory excursion of the lung is greatest.

The duration of friction is quite variable. It is often present at one examination and absent at the next; or, on the other hand, either the same sound or newer ones may persist with remarkable intensity for many days after pain and all other symptoms of the affection have entirely disappeared.

Serofibrinous Pleurisy.

Definition.—Serofibronous pleurisy or pleurisy with effusion is an inflammation of the pleura attended with both a fibrinous and a serous exudate.

Etiology.

Serofibrinous pleurisy has always been regarded, in the vast majority of cases, as a primary idiopathic disease, but though it is unquestionably true that its clinical relation to other conditions is still difficult to determine, few cases can now be recognized as genuinely idiopathic.

Great interest attaches to the etiology of these seemingly primary forms; and happily the medical progress of the last few years, and especially the bacteriological researches of a host of careful workers, have materially widened our knowledge in this field. It is only a short time since a large proportion of all pleurisies were attributed to cold; at present it is seriously questioned by many authorities whether there is such a thing as pleurisy *a frigore;* not that the influence of cold is wholly denied—this would be doing violence to the facts of daily observation—but it is now quite universally maintained, and with probable truth, that cold, though perhaps the most important of all exciting causes, is never more than this. This is now the expressed belief of Huguenin, Landouzy, Kelsch and Vail-

lard, Netter, von Ziemssen, and undoubtedly also the majority of other observers.

One of the chief reasons for this recent change of opinion is the apparent relation between many cases of primary pleurisy and tuberculosis. The very great importance of any such relation, once established, is sufficient to warrant an extended consideration of all the evidence in hand. Following somewhat closely the path laid out by Netter in his article in the "Traité de Médecine," we may marshal our facts as follows:

1st. *Antecedents, both Family and Personal.*—The evidence here is little more than suggestive. Engster, in 163 cases of primary pleurisy, obtained a personal history of tuberculosis in only 21; Netter found antecedent tuberculous manifestations in 11 out of 50 cases thus examined; of 58 cases of effusion Osler obtained a tuberculous family history in 21. Of themselves these facts have but little value.

2d. *The Future of Pleuritics.*—If it can be shown that a considerable proportion of those who have had one or more attacks of primary serofibrinous pleurisy subsequently develop a distinct form of tuberculosis, the evidence thus afforded must be allowed to be of incontestable value. It must also be granted, as is so strongly insisted upon by Netter, that negative statistics have but little worth as against even a small amount of positive evidence; there are so many possible sources of error when, for example, it is stated that of a given series of effusions nearly all of the persons have continued in perfect health. Following are some of the more careful observations as to the subsequent history of pleuritics: Handford reports 5 cases of effusion in apparently well subjects, 3 of whom afterwards became tuberculous. Fiedler had 112 cases, of which 25 subsequently died of tuberculosis, and 66 others became tuberculous. Barrs ascertained in 1890 the condition of 57 cases treated at the Infirmary of Leeds from 1880 to 1885; 21 had died of tuberculosis. V. Y. Bowditch investigated in 1889 the subsequent history of 90 patients treated for effusion by the elder Bowditch from 1849 to 1879; 30 had died of tuberculosis and 1 at least of those still living was tuberculous. Ricochon was able to follow carefully 32 cases of pleurisy *a frigore* in private practice; tuberculosis developed sooner or later in all but 2. A. Smith saw 2 instances of tuberculosis in 4 cases of primary effusion observed in private practice.

Many similar series of cases have been reported. Those selected, while showing a far greater proportion of subsequent tuberculosis than many others, are at the same time the most trustworthy at command. They represent cases seen in both hospital and private practice. Taken together they give a total of 310 cases of pleurisy

with 178 instances of subsequent tuberculosis, or 57 per cent. This is probably above the truth. Sears, who collected a still larger number of reported series, found an average of only 39 per cent. At all events it seems safe to affirm that at least 30 per cent. of all cases of serofibrinous effusion will eventually succumb to some tuberculous affection.

3d. *Microscopical examinations* of the pleural exudate, as well as cultures, have proved relatively barren of results. It is now universally admitted, in view of the careful investigations of Prudden, E. Grawitz, Ehrlich, Ferdinand, Levy, and others, that tubercle bacilli are not found in the very great majority of even those pleurisies which occur in tuberculous individuals. For example, Ehrlich found the bacillus in only 2 of 9 phthisical cases examined, and Levy obtained a negative result in all of 13 similar cases. Lemoine made cultures from 38 cases of serofibrinous pleurisy, and found that 28 were sterile; and yet 15 of these sterile cases afterwards furnished foci for tuberculous invasion. Since other bacteria are usually found in non-tuberculous pleurisies a negative result is even regarded by many (Netter, Vaillard) as strong presumptive evidence of tuberculosis.

4th. *Inoculation of animals*, usually peritoneal with the pleural exudate, has been more fruitful. Pansini made inoculations from 15 cases; 6 of these produced tuberculosis, while in 3 was found only the pneumococcus and in 1 the streptococcus.

Netter inoculated from three series of effusions: First from 16 cases in individuals known to be tuberculous; only 8 positive results were obtained; second, from 25 cases *a frigore;* in no less than 10 or 40 per cent., the results were positive; third, in 14 cases in which the pleurisy was satisfactorily explained on other grounds, and all were negative. Netter therefore believes that at least 40 per cent. of all primary exudates contain the tubercle bacillus; and the fact that even the first series gave but 50 per cent. of positive results would indicate that the actual proportion is much higher.

5th. *The Effect of Tuberculin.*—The only instance of this test is quoted by Netter from the report of the Prussian Government: 15 cases of pleurisy were injected, with both local and general reaction in 13; since of healthy individuals only 8.5 per cent. react, this evidence, though meagre, is of considerable value.

These various facts and sources of evidence need no comment. They demonstrate, as Netter says, that in serofibrinous pleurisy tuberculosis is the causative factor most frequently met with. A conservative estimate would be 35 per cent. As to whether or not most of these pleurisies are really tuberculous, in the sense that the se-

rous membrane is the seat of a tuberculous process, is not yet known. Kelsch and Vaillard claim to have invariably discovered tubercles in all such pleuræ examined. Osler emphasizes the frequency with which tubercles are overlooked, but found them himself in only 32 per cent. of 101 cases examined. Much study will be requisite before the exact anatomical relation between primary pleurisy and tuberculosis is definitely determined.

Other causes of primary pleurisy may be classified as follows:

a. Rheumatism, perhaps the most frequent cause after tuberculosis, although this is a question upon which opinions differ. Some good authorities hold that the rare coincidence of pleurisy with articular rheumatism is strongly opposed to this supposition. Fiedler, while regarding the relation of the two as intimate, believes the port of entry of the poison to be very often a rheumatic angina; Hueguenin thinks pleurisy is often the sole manifestation of rheumatism, and usually bilateral; Netter has seen it oftenest in connection with articular rheumatism, or just preceding the articular attack. In general, most authorities recognize a rheumatic form of serofibrinous pleurisy, although the exact materia peccans is not yet known.

b. The Pneumococcus.—Most of the so-called metapneumonic effusions are purulent; according to Netter's own experience, 18 out of 22. Still the serofibrinous form is not so very infrequent, both with and following croupous and catarrhal pneumonia. The exudate may be sterile; but in a very considerable number Fraenkel's diplococcus has been found, often in pure culture. For example, in 6 metapneumonic cases examined, Prudden found the pneumococcus in 2. E. Levy examined 10 cases accompanying pneumonia and influenza; he found the pneumococcus in 6, staphylococcus pyogenes in 1, streptococcus in 1, and in 2 the results were negative. We have mentioned Pansini's series of inoculations from 15 serofibrinous cases; 3 of these were pneumococcal.

It seems, therefore, highly probable that the majority of effusions accompanying pneumonia are due to Fraenkel's diplococcus. But this same germ has in several instances been found in effusions which were apparently primary and quite independent of any pulmonary affection. Hueguenin recognizes such a form, and thinks that the pneumococcus may make its way from the buccal cavity to the pleura without involving the lung.

c. Syphilis.—According to Pretorius this cause is by no means uncommon; he states that pleurisy may either be an early tertiary lesion, or attend the roseola of the secondary stage as described by Chantemesse and Vidal. Talamon also recognizes both a secondary and a tertiary form. Rochon admits a primary

pleurisy which appears with the eruption, but regards the so-called tertiary form as merely secondary to other contiguous tertiary lesions.

d. The Acute Infectious Diseases.—The Eberth bacillus of typhoid has been found in pleural effusions by a number of different observers. Charrin and Roger report a sero-hemorrhagic effusion in which this bacillus was found in pure culture; the patient had rose spots and the general symptoms of typhoid, but the autopsy showed no intestinal lesions. Sahli and Fernet also report cases containing pure cultures of the typhoid bacillus; in the latter's there was complete recovery after the removal of the fluid.

Other infections, such as pyæmia and scarlet fever, are more often followed by empyema than by the serous form, and such empyemas usually contain the regular pyogenic cocci; still serofibrinous pleurisies do occur in this class of diseases, and it is presumable that their cause is the same. Both the streptococcus and staphylococcus pyogenes have been found by Grawitz, Ferdinand, Levy, and others in simple serous exudates; such are apt to become eventually purulent, but not necessarily so. Goldschneider, for example, observed three cases containing the streptococcus, none of which afterwards suppurated.

e. Cardiac and renal disorders are not infrequently complicated by serofibrinous pleurisy, particularly in the aged. In cardiac cases the pleurisy is probably dependent, as a rule, upon pulmonary infarction. Levy found the staphylococcus aureus in all of four cases having this origin. Pleurisies in connection with Bright's disease have been attributed both to irritating substances in the blood and to microbes. Fraentzel's idea is that the pleura is simply rendered more vulnerable by the general cachexia.

Such are some of the factors which may be at work in cases of apparently idiopathic serofibrinous pleurisy. Other cases, fewer in number, are manifestly secondary to contiguous processes. Most prominent among these is trauma—either a simple contusion, or a fracture of a rib, or a penetrating wound. Also parietal affections, such as abscesses and tumors of the breast or axillary glands, erysipelas, and caries of the ribs or vertebræ. Effusion may furthermore be secondary to pericarditis, to malignant disease of the œsophagus or mediastinum, and to wounds of the œsophagus, as in the case of a penetrating fish bone reported by Laache. Abdominal affections may give rise to effusions, such as peritonitis, abscess and especially hydatids of the liver, appendicitis, and ovarian cysts, among fifty of which Demons found a serofibrinous pleurisy in no less than nine. Finally, an effusion is an almost invariable accompaniment of

pneumothorax and new growths of the pleura, as will be further considered in treating of these affections.

Pleurisy with effusion is a disease of all ages; it is not infrequently met with at both extremes of life, and in children particularly it has come to be recognized as of common occurrence. According to Netter, and to Engster, whose estimate is based upon a series of one hundred and forty-seven cases, the disease is most frequent in January and April, least so in September and October. Engster also found that it was about four times more common in men than in women, and Moutard-Martin reached nearly the same conclusion.

Pathological Anatomy.

At the outset of a serofibrinous pleurisy the pathological changes do not differ in any way from those of the fibrinous form already described. There are the same superficial capillary congestion, the same activity and multiplication of the connective-tissue cells just beneath the endothelial layer, and the same exudation of fibrin upon the free surface. Here also, in consequence of active proliferation of the connective-tissue cells, which push up through the endothelial covering into the coating of free lymph, there is a development upon the pleural surface of a layer of embryonic tissue containing newly formed blood-vessels and susceptible of such further transformation as has been already described under dry pleurisy. At a later stage we have to deal with a fibrinous pleurisy plus a considerable quantity of serous exudate, and with the subsequent changes which such a collection of fluid involves.

In the first place, the pleural walls attract attention. They are seen to be covered with a false membrane which may be either universal or deposited here and there in patches. The membrane is composed of coagulated fibrin containing in its meshes a few white and red blood corpuscles and epithelial cells. Much of this fibrin has its origin in the serous exudate which, as we shall presently see, contains it in considerable abundance when first produced; within a few hours coagulation takes place, and the separated fibrin is deposited upon the pleural surface. The membrane is of a white, whitish-yellow, or in older cases of a more brownish or grayish color. Its thickness varies greatly in different localities, in some places amounting to half an inch or even more. Its surface is usually rough and uneven; it is often villous and shaggy, and long filaments of fibrin may float out from it into the fluid or connect it with the opposite wall. At first the membrane is soft, and of more or less brittle consistence, like the boiled white of an egg; in older

cases it may become quite tough and elastic. When it is removed, the underlying pleural surface is found to present the reddish and granular layer of embryonic tissue which we have seen to be the common result of pleural inflammation.

The fluid exudate is found in exceedingly variable quantity, oftenest perhaps amounting to one to two pints, sometimes to a gallon or even more in a single pleural cavity. Its color in a fresh effusion is usually pale greenish-yellow or amber like that of urine; in an older one it is likely to have become much darker, a deeper or more brownish shade of yellow; in still other cases the color may vary from light red to almost black from the presence of more or less fresh or decomposed blood. The fluid is nearly always of limpid consistency. It is usually also clear and transparent, in its upper layers at least, although it may be varyingly clouded by the presence of leucocytes or of small particles of fibrin or fat. The coagulated fibrin which separates from the exudate soon after its production is deposited not only upon the walls, and upon the bands and adhesions which may unite the costal and pulmonary pleuræ, but also, especially when the exudate is particularly rich in fibrin, as free masses which swim in the liquid itself. These may be either in the form of large clumps and clots which sink to the bottom of the cavity, or of finer particles which float about when the fluid is disturbed, and give it an appearance of opacity. When leucocytes are present in sufficient quantity to produce the same effect, we reach the border line of empyema, between which and serofibrinous effusion there is no sharp anatomical distinction.

Other formed constituents of the fluid are: Red blood discs, present according to some in all effusions, though a recent study of forty-eight cases by Grawitz showed blood in only ten, eight of which were in tuberculous individuals; a few epithelial cells, often in a state of fatty degeneration; free fat, encountered occasionally in old effusions and sometimes in sufficient quantity to impart a decidedly milky appearance to the fluid (see Chylous Pleurisy); Charcot's crystals, a very rare constituent; and, finally, the various micro-organisms which have been already mentioned in the section on etiology.

Other physical and chemical characteristics of the pleuritic exudate have been studied by Frerichs, Winterich, Naunyn, Ewald, and especially by Mehu. It is generally conceded that its chemical constitution is almost identical with that of blood serum, except that there is a larger proportion of water. Its specific gravity may vary from 1.005 to 1.030, but is usually from 1.012 to 1.022. According to Mehu's analysis, the usual quantity of organic constituents is from five to six per cent.; among these are urea and uric acid (Naunyn),

biliverdin in certain cases, sometimes glycogen according to Eichhorst, fat and cholesterin, and especially fibrin and albumin. The usual proportion of fibrin is about 0.1 per cent., and it is believed by both Mehu and Laboulbène that those cases in which the effusions are richest in fibrin admit of the most favorable prognosis.

The position occupied by the fluid, and its exact contour—questions of vital importance as regards diagnosis and treatment—must, of course, vary exceedingly according to its quantity, the previous condition of the affected pleura and lung, and other factors which will be presently considered. If old adhesions have been left behind by previous pleurisies the position and shape of the fluid body will naturally be materially modified; thus are produced the various forms of encapsulated effusion, as, for example, the diaphragmatic, interlobar, and mediastinal, and the costopulmonary, varieties which are oftenest purulent, and will be again referred to. Sometimes the fluid collects in several communicating apartments formed by adhesions between the pulmonary and costal pleuræ—the so-called multilocular effusion; or, again, it may be exuded into the meshes of a false membrane—a form which has been termed areolar. And so, from these various causes, an effusion may be found in exceptional cases at any part of the pleural cavity, at the base or apex, in front or behind; and owing to the resulting atypical displacements of lung and other organs, a confusing and often misleading clinical complex may be produced. In the great majority of cases, however, an effusion is unhampered by preexisting pathological conditions of any great moment; and it seems to me, therefore, of considerable interest and value to consider at some length the various factors which govern what may be called the typical shape of a pleuritic effusion.

These factors are: 1. The force of gravity; 2. The normal cohesion between the opposite pleural surfaces; 3. The position of the patient while the exudation takes place; 4. The normal tension of the lung, and, to a less extent, of the mediastinum, diaphragm, and chest wall.

1. *Gravity.*—In spite of Garland's experiments, which seemed to show that the fluid always gathers first in the lower and inner portion of the pleural cavity, it is hard to believe that gravity is not the prime factor in determining its position. Garland's observations have never been confirmed, those of Ferber gave opposite results, and a more recent experiment of Dwight was likewise adverse; he injected the pleural cavity of a child lying with head and shoulders low, and found by a series of frozen sections that the fluid had collected in the upper portions of the thorax. Clinically there is

but little opportunity for comparative observation. During the formation of a pleuritic effusion the thorax is usually upright, never below the horizontal, and, as a matter of fact, the fluid is invariably found in its lower half.

It may at least be stated as extremely doubtful if under normal conditions there are any forces at work which are capable of overcoming that of gravity; and that gravity determines the position, though not necessarily the contour, of the effused serum.

2. *Cohesion.*—That a certain degree of cohesion exists normally between the costal and pulmonary pleuræ can hardly admit of doubt, although the results of experiments are conflicting. West assures us that pneumothorax does not invariably follow an experimental opening of the pleura; this certainly accords with the clinical observation of external wounds. Northrup, on the contrary, found that the lung always collapsed the instant the costal pleura was so much as pricked. Even if this be true, it would merely show that there is no force of cohesion sufficient to resist the retractile power of the lung; it still remains more than probable that some cohesion does exist between the opposite pleuræ. But admitting such a factor, its influence upon the position of a pleural effusion is difficult to prove, and is assuredly of subordinate interest. It very likely prevents the fluid from rising as high at the periphery as it would otherwise do; and it undoubtedly has much to do with the comparative immobility of pleuritic effusions on change of posture.

3. *Posture.*—Granting that the weight of the fluid is mainly responsible for its position in the lower rather than the upper region of the chest, of how much importance are minor variations in the posture of the patient during its formation? It is my belief that this influence is at most very small. The remarkable constancy of incipient effusion at the inner and posterior aspect of the chest, as shown by clinical observation, would seem to indicate that here other forces are at work which gravity is powerless to overcome. For example, I have never seen an effusion begin in the lower axilla; and I have observed but little difference in the height of the effusion, whether the patient had been constantly on his back or up and about during its formative stage.

4. *Pulmonary.*—Without doubt the most important of the various factors which determine the shape of the fluid body, and more especially of its upper surface, in which the clinician is chiefly interested, is the normal elasticity of the lung. At the risk of saying much that is elementary and universally understood, it seems not out of place briefly to consider here what must happen to the lung when the pleural cavity is invaded by a body of fluid.

Normally the lung is everywhere held in close apposition to the mediastinum, diaphragm, and thoracic wall by atmospheric pressure exerted upon the inner surface, so to speak, of the lung, the lower surface of the diaphragm, and the outer surface of the chest. All of these parts, being more or less elastic, are therefore normally in a state of constant tension, and the tension of each must be precisely equal to that of the others in order to maintain the equilibrium. Suppose, for example, the normal tension of the lung suddenly increased; the lung would immediately retract, and the diaphragm would be obliged to follow until with increased traction its own tension had attained that of the lung and the two parts were again in equilibrium. It is evident that in order to appreciate correctly the dynamic conditions which prevail in the chest we must speak of the retractile power, not only of the lung, but also of the diaphragm and chest wall; the mediastinum, being under equal negative pressure on both sides, is not normally in a state of tension.

It results from these considerations that the pressure within the pleural cavity itself is constantly negative; that is to say, the tension of the surrounding parts exerts a constant force of traction so that if the cavity be connected with the external atmosphere either directly or through a column of water, this force will operate to draw into it a certain quantity of air or water, as the case may be; and this suction will continue until the tension of the parts is exhausted, and the intrapleural pressure is no longer negative.

This accords fully with the result of experiment, as, for example, that of Garland, in which fluid was thus drawn into the pleural cavity of a dog; also with the clinical observation that after puncture even a considerable quantity of fluid will sometimes refuse to leave the chest without aspiration.

We may then affirm that the presence of even a minimum quantity of fluid in the pleural cavity—whether it has been drawn in through an artificial opening, as in the experiments of Garland, or is an exudation from the pleural capillaries—necessitates a relaxation in the tension not only of the lung, but also of the diaphragm and chest wall. The lung retracts more than the others only because of its greater elasticity. The mediastinum, too, cannot remain unaffected. Normally under the equal negative pressure of both pleural cavities, it is now subjected to an increased relative pressure upon the side containing fluid, and must move slightly in the opposite direction. This fact is of vital importance as explaining the early displacement of the heart which may often occur in pleuritic effusion. Certain authors (Powell, Garland) have laid great stress upon the assertion that the heart is not pushed towards the well side by the accumulating

fluid, but drawn over by the opposite lung. The point does not appear to be well taken. The mechanism of the displacement is clear; and since it is quite evident that the increased unilateral pressure would compel a movement of the mediastinum independently of the well lung, it can hardly be said to be drawn over by the latter.

We have seen that by virtue of its retractile power the lung voluntarily recedes before the accumulating fluid until its tension is exhausted and actual compression begins. What shape does the lung assume during this retraction, and what is the relation between it and the column of water? Does the latter simply take a hydrostatic level, and the lung accommodate itself to the fluid; or must the lung retract in a certain definite and constant way, thus compelling the fluid simply to appropriate the space left vacant? It would seem not only theoretically, but also from experience and clinical observation that the latter of these suppositions can alone be true. Theoretically it is quite inconceivable that the lung, as a highly elastic and greatly distended body, should not retract with more or less uniformity towards its centre; a conception of the upper level of fluid as horizontal would involve an extreme retraction of the lung along certain radii, and perhaps none at all along others.

An experiment, suggested by Garland, may be made by a very simple apparatus to illustrate partially the necessary behavior of the lung. All that is needed is a six-ounce bottle, with a wide opening and a well-fitting cork, and a toy balloon whistle. The stem of the balloon is fitted tightly to a hole in the cork; the balloon is then inserted into the bottle partly filled with water, and is inflated until all air is expelled from the bottle; this is then quickly and tightly corked. We now have a highly elastic body, like the lung, kept in a state of tension by negative pressure, communicating freely by its interior with the external atmosphere, and separated below from its containing wall by a column of fluid. Two things may now be observed. In the first place, the fluid does not materially alter its position or shape in whatever position the bottle may be placed; and secondly, the upper surface of the fluid is not level; the balloon still maintains a marked curve the convexity of which projects downwards into the fluid.

Again, the numerous experiments of Garland upon animals, consisting in the injection into the pleural cavity of various quantities of plaster of Paris and other hardening substances, all showed a certain uniformity in the moulds thus obtained. In none was the upper surface horizontal; in all the depth of the column of fluid was least at the spine and greatest in the region of the axilla. Finally, as will hereafter be more fully described under physical signs, it

has been the clinical experience of nearly all observers that the upper line of effusion flatness is never horizontal, but corresponds very closely, in many cases, to the casts obtained by Garland.

It may therefore be confidently affirmed that within certain limits the lung is obliged to retract along definite lines, and to assume a more or less definite and uniform shape according to the amount of retraction. This shape is but little influenced by the weight of the fluid; the latter simply occupies the space left vacant by the retracting lung. In short, the fluid adapts itself to the lung, and not the lung to the fluid.

It is, of course, true that as the volume of fluid increases, its weight becomes a factor of constantly increasing importance as regards the displacement of organs; it plays a large part in the extreme displacement of the mediastinum, and particularly that of the diaphragm, which is found in large effusions.

The *pathological condition of the lung* in serofibrinous pleurisy varies, as we have seen, according to the quantity of fluid, and the presence of antecedent disease or complications. Retracting, as it does, in typical cases towards its hilus, it is found in large effusions pressed upwards and backwards against the spine as a dark-red or grayish solid fleshy mass, perhaps hardly larger than the two fists. In fresh cases it may be simply atelectatic, and readily susceptible of reinflation; later it often becomes the seat of fibroid processes of pleurogenic origin, although in general it is remarkable how long a period may elapse before the lung completely loses its capacity of re-expansion. In some cases the lung contains but little blood, in others it is hyperæmic. Aside from various antecedent acute or chronic pathological conditions, it may rarely show disseminated spots of fresh pneumonic infiltration, as in the case reported by Serafini, in which both these pneumonic areas and the fluid contained the diplococcus of Fraenkel.

The *heart and other organs* are found variously displaced. We have seen that such displacement usually begins with the first appearance of fluid in the pleural cavity, but it is only when the latter has reached a considerable amount that the various dislocations become apparent; and not until positive pressure begins and two quarts or more of fluid have accumulated, do we find those extreme instances presently to be described. The mediastinum is, of course, pushed towards the opposite side. The heart follows, together with the great vessels, and this displacement is sometimes sufficient to produce a marked angle in the vena cava when it leaves the diaphragm, possibly also more or less obstruction. In the great majority of cases the heart is simply crowded over *en masse*, the

relative position of apex and base remaining unchanged. Whether, as taught by Trousseau, it is even actually twisted upon its axis, so that the apex is found in the region of the right nipple, seems to be extremely doubtful. Osler and other observers of large experience have never seen it, and it is certainly contrary to all clinical evidence.

Depression of the diaphragm does not reach an extreme degree until the quantity of fluid is very large. It may then entirely lose its arch, or its convexity may even look towards the abdomen. There is then a corresponding depression of the liver or spleen; the former is somewhat tilted laterally, not so much, however, but that the left lobe is likewise below its normal position. In a large effusion the diaphragm of the unaffected side is also somewhat depressed; the displacement of the mediastinum permits a relaxation of the parts composing the sound pleural cavity in which the diaphragm participates.

It remains to consider the possible anatomical results of serofibrinous pleurisy. Usually there is complete absorption of the fluid and false membranes with only moderate thickening of the pleura and abundant adhesions. Exceptionally, the formation of new membrane is so extensive, and the pleural thickening is so great, that absorption of the fluid exudate becomes in time impossible and it remains unchanged for years; or the fluid itself may disappear, but fibrinous clumps and masses at the bottom of the cavity may remain and subsequently undergo cheesy or, more rarely, calcareous degeneration; these so-called pleuroliths have been encountered as large as an orange. In other cases, usually tuberculous, the pleura undergoes a slow and steady process of proliferation—a process which may also follow dry pleurisy, but which is here much more frequent. Sooner or later this fibroid process invades the lung along the lymphatics of the interlobular septa; both lung and pleura subsequently contract and there is resulting deformity of the chest, with all the other conditions hereafter to be described under "pleural adhesions."

Symptoms.

Acute serofibrinous pleurisy differs but little in its early symptoms from many cases of the simple dry form, and there is no criterion by which a subsequent effusion can be predicted.

In a healthy, robust individual acute serofibrinous pleurisy is of rather violent onset. Its chief symptoms are pain in the chest, cough, dyspnœa, and a very considerable degree of constitutional disturbance. An initial rigor is rare; slight chilly sensations, which may persist for several days, are not infrequent.

Pain is usually sharp and lancinating from the very first; it may, however, begin as a simple feeling of soreness which later becomes more acute and localized. In some instances it is so severe as to cause threatening signs of collapse. The pain is felt oftenest just outside the nipple in the fifth or sixth interspace; exceptionally it may be located beneath the sternum, under the clavicle, in the supra- or infraspinous fossa, or in the abdomen. Its source was originally supposed to be the rubbing of the two pleural surfaces against each other; but the frequent occurrence of friction without pain, and in a different locality, contradicts this view; and many facts, as for example, the existence in pleurisy of *points douloureux*, seem to show that much of the pain at least is due to an involvement of the intercostal nerves; hence, possibly, its existence in the exceptional locations above noted. The pain is sometimes excited and always increased by pressure or by any movement which disturbs the parts, particularly deep inspiration and cough. Its duration is extremely variable; it often ceases, or at least becomes much less severe, by the end of two or three days, and only in the rarest instances does it survive the appearance of effusion. This fact has always been attributed to the presence of fluid between the inflamed pleural surfaces; Garland believes that it is a result of the diminished respiratory movement which the effusion entails.

Dyspnœa is a very constant symptom of pleurisy, but its degree varies extremely in different cases. Due at first partly to the pain caused by full inspirations and partly to the fever, its severity will be directly proportionate to that of these signs. Soon, however, another element is added, that of pulmonary retraction before the growing effusion, and consequent diminution of aërating surface; and later also interference with the circulation from actual pressure upon the heart and great vessels. It is quite common, therefore, as the effusion progresses, to meet with a high degree of orthopnœa and cyanosis; the recumbent posture becomes impossible, and the accessory muscles of respiration are all brought into play. But the degree of dyspnœa is often strikingly out of proportion to the amount of fluid; in a very large effusion it may be slight even when fever is high, while in a small effusion it may even amount to orthopnœa. These differences depend both upon the previous state of the lung and upon the general nutrition; a diseased lung may be made but little worse by retraction or even compression, and the susceptibility of the respiratory centre to diminished oxygenation is largely dependent on whether the individual is robust or has been for a long time weak and cachectic. Thus in the very young or old, and in victims of chronic Bright's disease and the like, but little dyspnœa may be

provoked by the largest effusion. Again, an effusion which is rapidly produced is more apt to cause extreme dyspnœa than when the exudation is one which is slowly formed; in the latter an opportunity is given for more effectual adaptation to the new conditions. In general the duration of the dyspnœa is coincident with that of the effusion.

Cough is usually troublesome from the outset. It is short, dry, painful, and ineffectual, expectoration being very slight or absent. At first due to pleural irritation or a slight bronchitis (Nothnagel), it afterwards changes its character, becomes more paroxysmal, and is often induced by changes of posture, as from the recumbent to the sitting; this is attributed by Peter to an irritation of the ends of the vagus caused by displacement of fluid, an explanation which is not, however, accepted by Nothnagel or Fraentzel. During absorption of the exudate cough may perhaps result from reexpansion of the lung, as is so often seen during aspiration.

The posture of the patient during the initial stage is the same as in dry pleurisy; if there is no orthopnœa, he either lies on the well side to avoid pressure, or in a semirotated position towards the affected side. As soon as any considerable effusion has developed, the posture changes; the patient now lies upon the affected side in order to give freer play to the well lung, the respiratory function of the compressed lung being in complete abeyance.

The constitutional symptoms are usually marked when the disease is primary and acute. After a few hours, possibly, of malaise, there is an abrupt rise of temperature to 102–104° F., generally without chill, and attended by the usual headache, anorexia, furred tongue, muscular pains, and other accompaniments of fever. The fever varies exceedingly in different cases. Most authors give as more or less typical a steady continued fever of 102° to 103° or even 104° for from seven to ten days; it then becomes remittent with gradually diminishing evening exacerbation until at the end of another week it has fallen to the normal. But there is certainly frequent divergence from this type. The initial high temperature may almost immediately subside, or a slight hectic fever may continue until the effusion is entirely absorbed. In general the persistence of any considerable fever is evidence of a continuance of the inflammatory process.

The pulse in serofibrinous pleurisy, besides the frequency which would naturally result from the fever, is apt to be small and hard. Netter states that these latter characteristics are due to pain, and disappear with the subsidence of the latter; Fraentzel says that they become more noticeable as the effusion increases and are due to di-

rect interference with the return of venous blood to the heart; the view that this, rather than a diminished circulation of blood in the compressed lung, is the cause of these phenomena, he regards as corroborated by the fact that after aspiration the pulse often becomes immediately full and soft, although the lung as yet cannot possibly have expanded.

The urine is at first scanty and high-colored, and usually continues so until the effusion begins to subside, when it may suddenly increase to a quantity far above the normal, and contain an abundance of chlorides which had hitherto been diminished.

The total duration of an acute serofibrinous effusion, as above described, is, on an average, from one to two months. It is claimed by Lancereaux—and my own experience would seem to accord with this—that the affection does not lack a certain cyclical character. He speaks of a period of exudation, a period of quiescence—*période d'état*—during which the effusion remains at about the same height, and a period of absorption. Each of these periods is said to last about ten days, though, of course, a much longer time will often elapse from the beginning of absorption before all traces of the exudate have entirely disappeared. My own observation has been that the great majority of effusions are small, or at most moderate in size; and that in such a more or less typical course like the above is at least a very common occurrence. If this is a true conception, it is, as will later appear, of the greatest moment as regards the operative management of the disease.

Chronic and latent serofibrinous pleurisies form a group quite distinct from the foregoing. The terms chronic and latent are not, however, synonymous. Any acute pleurisy may become chronic; the effusion may simply persist without appreciable exacerbations of the inflammatory process, or there may be a series of acute febrile attacks, each one of which is attended by fresh exudation of serum; in either event the pleura is undergoing a gradual process of chronic thickening probably with secondary fibroid invasion of the lung. The latent form, on the other hand, is chronic from the start. It develops without pain, fever, or respiratory disturbance; its onset and progress are so insidious that the patient may be for a long time unaware of any thoracic trouble. But sooner or later certain symptoms do appear which lead him to seek advice. He has grown pallid, and complains of weakness, or of dyspnœa especially on exertion, or possibly of a sense of soreness, or uneasiness, or weight in the chest. His appetite is gone, and his flesh has begun to disappear. Such are the symptoms, perhaps not even suggesting any respiratory affection, which usually bring these cases of latent

effusion to the physician. Especially common in children in whom emaciation and pallor are often the only prominent signs, and in those of naturally or otherwise feeble constitution, the importance from a clinical point of view of this latent form can hardly be exaggerated. According to Pretorius the secondary syphilitic forms of effusion are very apt to pursue this course.

A very great proportion, some would say all, of these chronic and latent forms are tuberculous—that is to say, cases of genuine pleural tuberculosis whether associated or not with pulmonary phthisis. With the lapse of time, perhaps of many years, they all tend to produce marked and characteristic deformity of the chest through contraction of the newly formed connective tissue in both pleura and lung. The affected side is shrunken, especially in the lower half, the intercostal spaces are narrowed, the shoulder droops, there is lateral curvature of the spine, and the angle of the scapula is slightly tilted outwards and projecting. The general condition and respiratory symptoms of such individuals will be again referred to in the paragraph on chronic adhesions.

Physical Signs.

Until fluid has developed in sufficient quantity for detection, the physical signs of serofibrinous pleurisy do not differ in any way from those of the dry form. Practically the only sign of any importance is friction, a full description of which has already been given.

The effusion probably begins to form within a few hours from the onset of the disease; in the experiments of Andral and Wintrich with the injection of irritants into the pleural cavity of animals, this period varied from five to thirty hours. But it is not until considerably later, perhaps from the second to the fifth day, that the effusion can usually be detected. The quantity of fluid which may gather before any physical signs are produced has been variously estimated by different observers. It is usually stated at from 300 to 500 c.c. This will of course depend much on the methods employed.

That even 500 c.c. may not be sufficient to produce any perceptible dulness was recently demonstrated in one of my own cases. On my regular hospital round I made a careful examination of the chest of a man supposed to have chronic nephritis; the lower border of each lung behind was percussed and marked with all possible care; no sign of effusion was discovered, and auscultation was also negative. I had no sooner left the ward than I was hastily recalled and found that the man had suddenly dropped dead. The autopsy showed to my great surprise 750 c.c. of non-encapsulated fluid in the right pleural cavity; that this was not a post-mortem transudation is measurably certain, because of its unilateral character. In this case, however, there

was no examination with reference to the respiratory excursion; and it is quite probable that by this or other of the finer methods of diagnosis a much smaller effusion could have been recognized.

For greater convenience in description and also because of certain corresponding changes in the physical signs which will presently be considered, we may with advantage divide effusions according to their size into small, moderate, and large. In a small effusion the signs of exudation appear only behind; in the moderate form the pleural cavity is perhaps half-full of fluid, and flatness appears over the lower front; in a large effusion the lung is compressed, the mediastinum and diaphragm are much displaced, and the fluid nearly or quite fills the chest. We will first consider only typical uncomplicated cases of serofibrinous pleurisy.

Inspection.—Previous to the development of effusion and even when the latter has been produced in only small quantity, no change in the thorax is perceptible to the eye except a certain degree of diminution in the respiratory movement of the affected side; this is due, partly at least, to the pain. As the effusion increases, this respiratory immobility becomes greater; and finally, with complete filling of the chest, all movement of the affected side may cease.

The affected side is manifestly larger than the other. The nipple and scapula are both farther removed from the median line, and the sternum also is often slightly deflected towards the affected side, as may be tested by a string carried from the sternal notch to the symphysis. The intercostal spaces are seen to be more or less obliterated, rarely, perhaps, to protrude. The impulse of the heart's apex may be detected in an abnormal situation; or a noticeable tumor may be produced in the hypochondrium from sagging of the diaphragm or prominence of the dislocated liver. As hardly more than curiosities are to be regarded the one or two reported instances of the pointing of a serofibrinous effusion. In a case reported by Sahli a tumor appeared under the clavicle, but did not result in perforation. In another case, reported by the same author, a serofibrinous effusion was evacuated by vomica; Sahli could find but one other case mentioned in the literature.

Mensuration has always been much employed in the diagnosis of pleuritic effusion, but its value is extremely limited. The comparative measurement of the two sides rarely gives conclusive evidence, the difference being usually so slight as to be easily attributable to error; moreover, the normal difference of 1 to 2 cm. in the circumference of the two sides, usually in favor of the right, does not lessen the uncertainty of the result. On the other hand, as an indication of change in the quantity of fluid from day to day, repeated

measurements of the whole circumference of the chest may be of service. Still even here the results are not conclusive; as pointed out by Fraentzel, an effusion may be steadily diminishing and yet the chest circumference may remain unchanged, since the diaphragm is usually the first to feel the effects of absorption.

Palpation.—The most valuable of the signs furnished by palpation is the almost invariable diminution of vocal fremitus over that portion of the chest where the fluid is in immediate contact with the chest wall. It is hardly necessary to say that here as elsewhere the degree of fremitus, owing to great variations in different individuals, can be determined only by carefully comparing corresponding areas on both sides of the chest. In a small effusion fremitus over the fluid is only diminished; in a moderate or large effusion it may be totally absent. Few signs of effusion are more valuable than absence of vocal fremitus. Still it is not infallible. If there are numerous adhesions, or if the effusion is multilocular, fremitus is said to be frequently unimpaired; and that it may exceptionally be present in an apparently uncomplicated case of small effusion I can certify from a personal observation in which the diagnosis was confirmed by aspiration. Over the lung itself fremitus is normal if the effusion is only small or moderate; the line of demarcation between fluid and lung may be quite sharply defined by testing the fremitus with a single finger moved slowly from below upwards. In a large effusion fremitus is usually considerably increased over the lung because of its solidified condition.

Palpation may also, in a large effusion, disclose an increased sense of resistance in the intercostal spaces of the affected side. French authors speak of a sense of fluctuation which may be obtained by palpation with two fingers in the same intercostal space; it is, however, admitted to be of very rare occurrence. Mouisset further describes a "*sensation de flot,*" called also by Tripier "*fluctuation vibratoire,*" a sort of fremitus or vibratory sensation felt in the hand on applying it rather forcibly to the chest, or on laying one hand upon the chest in front and striking with the other behind. It is said to be perceptible only over a large non-encapsulated effusion in a subject with thin and elastic chest walls.

Other valuable evidence afforded by palpation is that of displacement of organs. In a large left-sided effusion, the heart's impulse may be felt in the epigastrium and also at times in the fourth and fifth intercostal spaces a few centimetres to the right of the sternum. In effusion upon the right side the impulse may be from 3 to 6 cm. or more outside the left mammary line. In small effusions cardiac displacement is best shown by percussion. Dislocations of the liver or

spleen, as produced by large effusions, are also most readily determined by palpation; either organ may project a varying distance below the ribs, or in extreme cases the diaphragm may even sag downwards and appear in the hypochondrium as a large, prominent, and fluctuating tumor beneath which on the right the whole liver may be felt (Fraentzel).

Finally, palpation may occasionally be of service in disclosing an œdema of the chest wall, which, however, appears only exceptionally in serofibrinous effusions, and in a very mild degree.

Percussion.—Wherever a pleuritic effusion is in contact with the chest wall the percussion note is absolutely flat; and a marked sense of resistance is imparted to the plessimeter finger.

The shape of this flat area, more particularly its upper border, has always been a fertile subject of discussion among clinicians. Owing largely, no doubt, to the divergence of opinion which still prevails, most authors refuse to accord any very prominent place among the signs of pleurisy to the curve of effusion. Up to the time of Damoiseau it was universally thought that the upper boundary of the flat area was horizontal. Damoiseau claimed that it was a parabola having its highest point at the angle of the scapula. The observations of Calvin Ellis, published in the later seventies, were somewhat similar. He described a curve having its highest point in the axilla, but quite different in shape from a parabola, and named afterwards by Garland the "letter of S curve." Garland also gave much study to the physics of the subject; and his work on pneumodynamics represents the best that has yet been presented to the profession on the relation between a pleuritic effusion and the surrounding organs. Both Ellis and Garland claim that all effusions except the very large ones, present the S curve.

German authorities, with a few exceptions, give the subject but little attention. Heitler described a curve very similar to that of Ellis. Fraentzel says nothing about the matter except as to very large effusions which nearly fill the chest. Wintrich states that the line is not horizontal but descends towards the ground at a more or less acute angle. Leichtenstern and Ferber think it depends upon the posture of the patient early in the disease. Gerhardt holds the same view. Weil is more explicit; he finds that small and moderate effusions usually present a curve with upward convexity which is highest at the spine. He adds, however, the following important confirmation of the opinion expressed by Ellis: "In other cases I was able to convince myself most emphatically that the exudation occupied almost the whole lateral region of the thorax; while in front it was scarcely perceptible and behind did not reach as high as in the mid-

dle axillary line." Since this statement covers the really important points of the S curve, it is difficult to understand his assertion made further on, that he has never been able to convince himself of the reality of the S curve. Netter adopts the parabola as originally described by Damoiseau.

These differences of opinion are not easy to explain. Varied methods of percussion may account for them in part. Undoubtedly the main reason is to be found in the fact—for me, at least, assured—that *these curves vary with the quantity of fluid.* This does not, however, impair in any way their diagnostic value. Each curve is quite constant and characteristic in its own particular field; and I venture to affirm that no other one sign of effusion is to be compared with this in diagnostic importance and utility.

One word in regard to method. The curve in question represents the upper border of absolute flatness; and this can only be determined by light percussion. The lung above the fluid is not fully resonant—especially behind—and the stroke must be exceedingly light and delicate to differentiate accurately between this pulmonary dulness and the absolute flatness below.

Before enough fluid has collected to give rise to flatness, the commencement of effusion may be suggested by a slight, illy defined dulness at the extreme base behind; or, as emphasized by Weil, by a diminished respiratory excursion of the posterior pulmonary margin.

Small Effusion.

The first positive sign of a small collection of fluid is a zone of flatness which appears at the extreme posterior base of the chest. This zone is at the outset not more than two to three inches in height, and is frequently overlooked by those who fail to mark carefully the lower pulmonary limits in all examinations of the chest. Remembering that this limit upon the left is normally about an inch lower than upon the right, any greater difference between the two will at once arouse suspicion and lead to further investigation. The upper border of this zone is a curve which may be termed the "convex curve" of small effusion. Beginning at the spine the line extends at first outwards, then more abruptly downwards so as to reach the base at about the posterior axillary line. As the fluid increases in quantity this zone widens and the drop may be farther forwards. The latter is not, however, invariably the case; it would seem that posture is not entirely without influence upon the shape of this flat area; and not infrequently this zone may be five to six inches in width and yet not reach further forward than the middle axillary line.

This "convex curve" is extremely constant. I have never yet

seen a different one in small non-encapsulated effusions, such as have formed at least three-quarters of my own cases; in most instances the diagnosis was confirmed by exploratory puncture.

The percussion note over the lung in small effusions is comparatively unchanged; resonance may occasionally be a trifle increased and very slightly tympanitic. As a rule the heart is not perceptibly displaced.

Moderate Effusion.

After a growing effusion has reached a certain height behind, any further increase is no longer upwards but outwards and forwards into the axilla. It is now marked above by the "letter of S curve," as originally described by Ellis. Beginning at the spine, this line passes first outwards, then upwards by a gentle curve to the upper axilla or the shoulder joint; from this point it may drop in front to the base near the apex of the heart; or in a larger effusion it may follow approximately the course of the fifth or fourth rib to the sternum. Usually the change from the convex to the S curve is too abrupt to be accurately followed; flatness suddenly appears in the axilla, and the S-form has developed between two successive examinations. During the past year, however, I have attended a case of effusion in which the fluid remained for several days at a half-way point. This curve, which I had the opportunity of verifying at a number of different visits, may be represented in imagination by a moderate bulging of the convex curve in the direction of the upper axilla.

The lung above a moderate effusion gives a resonance which differs according as percussion is made in front or behind. Posteriorly it is decidedly dull. This is more marked as the line of fluid is approached, and is especially noticeable in the space between the S curve and the spine. Garland calls this space the "dull triangle," and recommends that it be cleared somewhat by means of a few deep inspirations before attempting to mark out the curve. This is undoubtedly a valuable suggestion; personally I have never found it necessary, and it should not lead to the inference that this curve is often obscure or difficult to detect. In front, resonance over the lung is markedly tympanitic; its pitch is low at first but becomes higher as the effusion increases. Both Fraentzel and Weil regard the appearance of high-pitched tympany as indicative of beginning compression. This tympanitic resonance over the retracted lung of pleuritic effusion is usually termed the *bruit skodique* after Skoda and is probably due to the diminished tension of the alveolar walls. On the other hand, diminution in volume means increased density and there-

fore higher pitch; hence the gradual change from a low to a high tympanitic note as the lung begins to undergo actual compression by the fluid.

In moderate effusion the heart alone gives evidence of displacement, and this only when the effusion is in the left pleural cavity. Any movement of the heart toward the right is extremely easy to detect. Normally the right border of the heart is represented by a perpendicular line extending from the third rib to the liver just inside the left border of the sternum. The lower half of the sternum is normally resonant, at least as resonant as its upper half, with which it should always be compared. Any displacement of the heart towards the right is at once attended by the appearance of dulness in this cardiohepatic angle; and because of the sharp differentiation between flatness and full resonance which is here possible, any encroachment upon the sternum is very easily detected. This slight displacement of the heart is an important confirmatory sign of left-sided effusion. Of course enlargement of the right heart, or a pericardial effusion, will produce a like result, and both must therefore be excluded. In children from the fifth year to beyond puberty the sign has no value, since here the præcordia extends normally beyond the right sternal margin.

Large Effusion.

Here the shape of the effusion no longer has the same diagnostic importance as in the smaller forms. The curve is hardly as characteristic, and in the marked displacement of organs we now have a far more absolute sign. Again, the line is not always easily defined, particularly behind where the resonance over the compressed lung is at most very dull. Still the curve of large effusion is very constant. Beginning at the junction of the second or third rib with the sternum, it passes outwards and upwards over the clavicle and shoulder, then downwards and inwards to the fifth or sixth dorsal vertebra. It has an upward concavity, and may be termed the "concave curve" of large effusion in contradistinction to those already described.

In front, resonance over the compressed lung is still tympanitic and of high pitch. Behind it is very dull, sometimes quite flat; indeed the lung may be wholly separated by fluid from the posterior wall of the chest.

Several special varieties of resonance are to be noted as of occasional occurrence over the compressed lung in front. Just below the inner end of the clavicle the note is often tympanitic, even when this quality has disappeared below and when the rest of the lung is quite dull or flat. It is then called the "Williams' tracheal tone," and

originates in the large bronchi or trachea, the vibrations of which are transmitted through the compressed lung. This tone has a high pitch which changes with opening or closing of the mouth; it can be detected only by strong percussion, and is found only in very large effusions. Rarely it has a more or less metallic quality or "cracked-metal" resonance—the *bruit de pot fêlé*—due probably to some local constriction of the bronchus.

The *dislocation of organs* is perhaps the most important of all the evidences of large effusion and must be made out chiefly by percussion.

The heart, if free to yield to the pressure of the fluid, is found displaced to the right or left as the case may be. This dislocation is far more pronounced when towards the right. We have already seen that even in moderate effusion upon the left there is a movement of the heart towards the opposite side, as indicated by the appearance of dulness over the lower half of the sternum. As the fluid increases, the upper and right boundary of this dulness moves still further outwards, and the dulness becomes more complete. Finally, in very large effusions the precordial area may lie wholly to the right of the median line and present an outline very similar to that which normally exists upon the left. It has both a zone of relative dulness and one of absolute flatness. The latter, continuous towards the left with the effusion and below with the liver, is bounded above and to the right by a curved line with upward convexity, which extends from the costosternal articulation of the fourth rib outwards and downwards to the liver a little inside the mammary line. Outside of this flat area is the zone of relative dulness, about one inch in width. In right-sided effusion the outer borders of both absolute and relative cardiac dulness are simply displaced towards the left—in extreme cases so as to reach the anterior axillary line; the upper border remains at its normal level. These dislocations to the left are neither so pronounced nor so early perceptible as those towards the right, and have therefore an inferior diagnostic value.

With the heart the mediastinum also is crowded over towards the sound side. This displacement can only become plainly evident when the fluid has risen above the level of the fourth rib in front and the resonance over the lung has become quite dull, for then only is there a distinct line of demarcation between the sound lung and the diminished resonance or flatness of the opposite side. The mediastinum may be found at the sternal border, or, in extreme cases, even an inch or more beyond.

The downward displacement of the diaphragm can, on the left side, be followed with more or less accuracy; on the right it can only be

inferred from the position of the lower margin of the liver. Weil states that in small effusions, when the weight of fluid presses chiefly upon the posterior regions of the diaphragm, he has often detected an elevation of this lower hepatic margin, the upper boundary remaining unchanged—a condition which he ascribes to a tilting of the organ upon its transverse axis. In all large effusions the liver is depressed *in toto* and its lower border may even be found at a level with the umbilicus. At the same time there is usually a lateral tilting upon its anteroposterior axis, so that the left lobe is relatively higher than the right and the lower margin has an unusually diagonal course. In large effusions the upper hepatic boundary is of course blended with the flatness of the fluid.

It was stated that on the left the descent of the diaphragm can be more closely followed. This is true only in front, and here in a small area known as Traube's semilunar space. This space is bounded below by the free border of the ribs, above by the left lobe of the liver, the pulmonary margin, and the spleen. The underlying stomach and colon, when empty, give this area normally a tympanitic resonance, which presents a sharp contrast to the non-tympanitic resonance above, or, still more, to the flatness of effusion. It is easy, therefore, to follow the progressive drop of the latter, and the narrowing of this space which begins when the effusion has reached a considerable size. This space may eventually become wholly obliterated; or the flatness may even project beyond the ribs in cases, mostly purulent, in which the diaphragm actually sags. Traube, and following him Fraentzel, attribute a very great diagnostic importance to this space and the signs it affords. Weil, however, very justly observes that these signs are late, and therefore of no assistance in small or moderate effusions where such aid is most needed—a large effusion presenting, in general, no especial difficulty in diagnosis. Moreover, this space is normally dull if the stomach or colon is full.

The spleen is dislocated forwards and downwards when the diaphragm is depressed, but this can seldom be determined by percussion, since its flatness becomes blended with that of the fluid.

The opposite lung is by no means unaffected by large effusion. The very considerable displacement of the mediastinum already described gives the lung together with the diaphragm of the unaffected side an opportunity to retract. The resonance, therefore, may be very markedly tympanitic over the whole opposite front; and if the effusion is on the left side the liver may be found more or less depressed from the same cause.

The question as to the *mobility* of a pleuritic effusion has been

much disputed. While there is still some difference of opinion, most authors (Fraentzel, Weil, Ferber, Garland) agree: 1. That very large effusions are immovable; 2. that moderate effusions do show a slight change of position after the lapse of several minutes; and 3. that the extent of this change rarely amounts to more than a single intercostal space. As to small effusions statements are meagre. Gerhardt thinks these are even more movable than the large ones and that an early effusion may sometimes be detected by a suspicious dulness which appears in the axillary region when the patient assumes the knee-elbow posture with inclination towards the affected side. I myself have never been able to detect the slightest change in the position of a small effusion.

Auscultation.—As a general rule, wherever the fluid of a pleuritic effusion is interposed between the ear and the lung, the respiratory murmur will be found to be diminished. In some cases it is totally absent, though this can hardly be considered a common occurrence. The cause of this diminished respiration is, on the one hand, the greater distance of the lung from the ear, and on the other the enfeebled expansion of the lung itself. The quality of respiration, as found over the fluid, is approximately vesicular in both small and moderate effusions, or, in other words, so long as the lung is uncompressed. When actual compression begins, and the entrance of air into the pulmonary vesicles becomes more impeded, the quality of the respiratory sound changes; it becomes at first bronchovesicular and finally bronchial after the tubes alone remain pervious. Hence over a large effusion vesicular respiration is never heard; if any at all is perceived it is bronchial—and usually by careful auscultation a very faint and distant respiratory sound can be detected which is bronchial in quality and becomes louder the closer the lung is approached.

To this rule, however, there are important exceptions. One of the more frequent of these is to hear loud bronchial respiration clear to the base of a large effusion—in children, especially, a very common occurrence. Less frequent are the instances in which respiration is bronchial over a small effusion, as, for example, when the posterior zone of flatness has a width of only three to four inches.

In still other cases there is complete silence over the whole chest from top to bottom—probably when from compression or other cause even the bronchi themselves are no longer open.

Respiration over the lung varies in the way that might be anticipated from the foregoing. In small effusions it is, though diminished, fairly distinct and of vesicular quality. In moderate effusion it is comparatively normal in front; behind it is distant and indistinct,

often called "indeterminate." In large effusions it is markedly bronchial as a rule, exceptionally quite absent. In certain instances also of the latter it may even be amphoric; here as with cracked-metal resonance, we can only suppose a constriction of the main bronchus.

The voice sounds are found to correspond in general with the respiratory murmur, presenting the same characteristics as to quality and intensity. For example, over a small effusion the voice becomes more distant the moment the stethoscope crosses the line of fluid. In a moderate effusion this change is still more marked, the voice is still more distant and perhaps somewhat plaintive in character. In a large effusion there is, as a rule, bronchophony over the compressed lung, and either distant or, rarely, loud bronchophony over the fluid. If respiration is totally absent the voice sounds are also faint and indistinct. Occasionally one hears a variety of bronchophony which has been supposed to have a deep significance in the diagnosis of effusion, and to which Laennec first gave the name ægophony. This sound is high pitched and has a bleating, quavering, or plaintive quality; as Laennec says, it has more the character of an echo than of the voice itself. It is far from a constant sign of effusion, and is generally heard only in certain phases of its development, oftenest, perhaps, when compression has begun but is not excessive. Besides being inconstant it is not even pathognomonic of effusion, being also heard at times over a consolidated lung. It is a sign which possesses considerable interest but is of no great clinical importance.

The whispered voice is usually transmitted through a serous effusion with great distinctness, as if the words were almost whispered into the ear. This "aphonic pectoriloquy" is often called Baccelli's sign, this author having laid particular stress upon it as distinctive of a simple serous exudate. It is now known to be neither constant in the latter nor peculiar to it; it is also found, though rarely, in empyema, especially in pneumonia, and very often in pulmonary cavities. Its diagnostic value is therefore very small.

Over the unaffected side respiration is likely to be louder and more puerile the larger the effusion and the greater the compensatory efforts of the sound lung.

Friction has already been referred to as an early and temporary sign of both dry and serofibrinous pleurisy. It usually ceases with the appearance of fluid, though it may exceptionally persist along its border from continued activity of the inflammatory process. In very rare instances friction may be heard directly over a small effusion, as is affirmed by Beck, and as has also occurred in my own experience in cases in which the diagnosis was confirmed by puncture.

I can merely state the fact without attempting an explanation. A variety of friction which may be termed pleuropericardial (Wintrich) is not infrequent; it is synchronous with the heart's action, and is produced by friction of the pleural covering of the pericardium against that of the adjacent lung. It is to be distinguished from genuine pericardial friction by its usual localization at the extreme left border of the præcordia, and by the presence also of pleural friction in its ordinary form.

The *reabsorption* of even a large pleuritic effusion may be complete. It seems unnecessary to describe again the different signs which mark the various stages of this process, since they all reappear in inverse order, but in character precisely similar to those above given. First, bronchial respiration appears, which becomes more and more vesicular and less distant until finally the full vesicular murmur is restored. So also with the sounds of the voice. The line of flatness gradually falls, passing though the same varieties of curve as in its ascent. Heart, mediastinum, and diaphragm again return by a succession of gradual changes to their former positions. One of the special signs of reabsorption is the appearance of friction of an intensity and extent such as are present at no other stage. It is also frequent to hear a fine crackling râle over the whole lung in front; the explanation of Traube that this râle is produced by the forcible entrance of air into the collapsed pulmonary alveoli may probably be accepted. Garland affirms that the effect of absorption is felt first by the diaphragm, then by the lung, and finally by the heart; the latter may, especially in left-sided effusions, remain permanently fixed in its abnormal position.

Although the progress of reabsorption is not difficult to follow when once thoroughly established, it is by no means easy to determine just when it begins; and yet this is of the greatest importance as regards treatment. Weil calls attention to the fact that it may be illusory to depend on percussion alone, particularly of the upper border of flatness. This may drop—as, for example, from yielding of the diaphragm—and yet the effusion be still increasing. On the other hand, the level of the fluid may remain absolutely unchanged and still a marked absorption have taken place, with corresponding return of diaphragm and mediastinum and reexpansion of the lung; as Weil says, one often sees no change whatever in the level of the fluid after the aspiration of a considerable quantity. Even if the fluid does sink, the presence of a thick deposit of lymph may cause the percussion note to remain unaltered. Mensuration is still less reliable. There is, in short, no positive sign of reabsorption, particularly of a large effusion. However, large effusions are at the present day rarely

left to nature; and in small or even moderate effusions I have always found that the careful percussion of the upper line of flatness behind is a reasonably safe guide; there is here so little displacement of organs that a diminution in the volume of fluid can hardly fail to show itself by a lessened area of flatness. In large effusions with marked displacements, a conclusion can be reached only by careful attention to details—such as, in addition to the fluid level, an increased width of Traube's space, a slight movement of the heart, or a rise of the liver. Here a careful marking of percussion outlines from day to day is of the utmost service.

For a long time after complete absorption of an effusion, a slight dulness with diminished respiration may persist at the extreme base of the chest behind. This suggests a residue of fibrinous clumps in the lowest portions of the pleural cavity, the absorption of which may be extremely slow.

For the physical signs of chronic pleural thickening with thoracic deformity, such as may result from all the different forms of pleurisy, the reader is referred to the section on chronic adhesions.

Purulent Pleurisy—Empyema.

Etiology.

Though the various pathological conditions with which empyema may be associated have long been known, the investigations of the past decennium have greatly widened our knowledge as to its primary and essential cause. It may now be unhesitatingly affirmed that every empyema is due to microbic invasion of the pleural cavity. Weichselbaum, in 1886, was among the first to discover the presence of the pyogenic microbes, the streptococcus and staphylococcus pyogenes, in the pus of empyema; in 1888 he also found the pneumococcus. In the same year the cocci of suppuration were found by Kracht in all of ten cases of empyema, and Fraenkel also made an important contribution to the same subject. In 1889 and 1890 further studies were made by Thue, of Christiania, and also by Marfan, Netter, Dreyfuss, Fraenkel, Brisac, Sarafini, Troisier, Woillez, Jaccoud, Türk, Leyden, and Kelsch. Since then, numerous investigators have entered the field, and have already given us some idea of the relative frequency of the different microbic forms of empyema and their clinical peculiarities. Among those to be prominently mentioned are Netter and Courtois-Suffit in France; Ehrlich, Levy, and Louis Ferdinand, in Germany; Pansini in Italy; and Koplik and Prudden in the United States.

Recent French writers upon pleurisy (Netter, Courtois-Suffit) have described the various etiological forms of empyema—streptococcal, pneumococcal, tuberculous, etc.—as entirely distinct affections. There is much to be said for this classification, and undoubtedly the time will come when such a division of the subject will be universally recognized. At present, however, when our knowledge is still incomplete and the diagnosis of these various forms is still impossible for the great majority of practising physicians, it would seem to correspond more to actual clinical requirements to consider empyema as an entity rather than as several distinct affections. I shall merely attempt in the following pages to state certain special traits of the different forms as given by Netter; not that they are to be regarded as fully established facts, but simply as a basis for further investigation.

We may then, following Netter, describe empyema as resulting from the invasion of the pleural cavity by the following microbes:

Streptococcus Pyogenes.—This appears to be by far the most common form in adults. L. Ferdinand, in 12 cases of empyema, found the streptococcus in 6, or 50 per cent.; one of these was a mixed infection with staphylococcus. Prudden, in 24 cases, found the streptococcus only 7 times, or 29 per cent.; however, it is not certain that all of these cases were of adults; there were 11 metapneumonic cases as against only 8 of "simple empyema," among which belong all of the 7 above mentioned. Netter's series is the largest and presumably, therefore, the most reliable; he found that in a total of 127 cases of empyema in adults, not excluding the tuberculous or putrid, 56, or 44 per cent., were streptococcal.

It seems, therefore, that of all cases of purulent pleurisy in adults, about forty per cent. are produced by the streptococcus. In children this form is only about half as frequent, the pneumococcus taking in them the most prominent position. As we have already seen, the streptococcus may also exist in serofibrinous pleurisies, and this would indicate that either the microbe must be present in very considerable numbers to cause suppuration, or else, as Netter suggests, there must be, in the immediate vicinity of the pleura, some focus whose soil is peculiarly adapted to their multiplication.

Streptococcus empyema is, in the great majority of cases, a secondary affection; where it appears to be primary, it is probable that the original focus of suppuration has been overlooked. Following are the various conditions to which it may be consecutive, as grouped by Netter in the order of their greatest frequency:

I. *Diseases of the Lung.*—Most important among these is *bronchopneumonia,* especially the form associated with influenza. Of Netter's

56 cases, 17 had this origin, and 3 others followed a bronchopneumonia of different origin. In 7 streptococcal cases examined by E. Grawitz 4 followed influenza, hence presumably bronchopneumonia, although it is probable that grippe may cause empyema without any intermediate affection of the lung. Other pulmonary sources of streptococcus empyema are *pneumonia, tuberculosis, bronchiectasis, gangrene, cancer,* and *pyœmic abscesses.*

II. *Diseases of the Mediastinum*—namely, *pericarditis,* cancer and other diseases of the *œsophagus,* and *abscess,* by propagation from the neck or otherwise, as in a case reported by Hanot, in which the original affection was a retropharyngeal abscess.

III. *Abdominal Diseases*—such as *puerperal peritonitis,* a very frequent cause, having been associated with eleven of Netter's cases; also the various *subphrenic suppurations,* as, for example, of the liver.

IV. *Infectious Diseases.—Scarlet fever, diphtheria, erysipelas,* and *puerperal fever.*

Still another possible source of streptococcus empyema is trauma; as, for example, aspiration, a cause which was undoubtedly much more frequent in former times when aseptic precautions were never observed.

In twelve of Netter's cases the empyema seemed to be primary. Netter, however, thinks that in many if not all of these there was some antecedent lesion of the lung.

The Pneumococcus of Fraenkel.—The pneumococcus may give rise to either primary or secondary forms of empyema. The latter are associated with pneumonia, and are usually termed metapneumonic. The primary form was first described by Netter in 1887, and has since come to be generally recognized. In what way the pneumococcus gains entrance to the pleura must remain a matter of conjecture. Netter thinks it quite possible that it may penetrate the walls of the pulmonary alveoli without necessarily causing a pneumonia. It might also be carried by the blood.

The relative frequency of this form may be estimated from the following: Netter, in a total of 156 cases of all forms of empyema, found the pneumococcus in 53, or a little more than a third. Levy, among 17 cases examined, found the pneumococcus in 9. Prudden found it 9 times in 24 cases.

These figures, however, represent the relative frequency of this form at all ages. If, now, we consider its occurrence in children and adults separately, it will at once appear that in the former an empyema is much more likely to be pneumococcal than in adults. Netter observed 127 cases in adults alone; of these, 32, or about 25 per cent., were pneumococcal; on the other hand, in 29 cases of children alone,

the pneumococcus was found in no less than 21, or nearly 75 per cent. of the whole number. Koplik reports 12 cases of empyema, presumably in children; the pneumococcus was present in 7.

This form is, therefore, about three times as frequent in children as in adults. From an analysis of two hundred and eighty-six cases of metapneumonic empyema made by Netter, it appears to be most frequent in the first decennium, about a third less frequent in the second and third, and extremely rare after the fifth.

As to the relative frequency of the primary and secondary forms, further statistics must be awaited. At present we have only those of Netter, who, in 53 pneumococcal cases at all ages, obtained evidence of an antecedent pneumonia in only 19. But it is to be remembered that 21 of these cases were in children, in whom a pneumonia may readily escape observation; and it is probable, as Netter says, that the great majority of pneumococcal empyemas are of secondary origin.

The Bacillus Tuberculosis.—Fewer cases of empyema are tuberculous than would be anticipated. Attention has already been called to the surprising fact which bacteriology has recently brought to light, that the great majority of all tuberculous pleurisies are serofibrinous. The following data may be given as to the frequency of the purulent form: In Netter's 156 cases, only 15 were tuberculous, or about 10 per cent.; from 12 of these 15 cases, inoculation was made with positive result in each case; microscopically, however, bacilli were found in only 5 of 13 thus examined, the others containing either the staphylococcus or no bacteria whatever. It appears, therefore, that while a positive diagnosis can be made only by inoculation, a microscopical examination will afford valuable evidence, either by demonstrating the Koch bacillus or by proving entirely negative. Other observers have examined only by culture and the microscope. For example: Prudden, in 24 cases, found the tubercle bacillus in 1 only; Ehrlich, in 19 cases, found the bacillus in 7, an unusually large proportion; Koplik, in 12 cases in children, found the bacillus in 1; L. Ferdinand, 12 cases, bacillus in 2; Levy, 54 cases, no bacilli.

Levy, Ferdinand, and Ziemssen all agree with Netter that the absence of all germs on microscopical and culture examination points to tuberculosis.

Other micro-organisms are comparatively infrequent. The *staphylococcus pyogenes* is, perhaps, the least so and particularly in association with other bacterial forms it is not so rarely encountered. Prudden met with 1 case in 24; Grawitz with 2 in 48 effusions of both forms; Koplik, 1 case in 12; Levy, 7 cases in 17; Netter, 6

cases in 156—all of these 6 were pure cultures; in 15 others the staphylococcus was also present, but mixed with other forms.

The sources of staphylococcus invasion in pure culture are, according to Netter: 1. Introduction of a foreign body into the pleura, the latter being either previously normal or already containing some form of effusion; 2. Other staphylococcal foci elsewhere in the body.

Thus, of Levy's 7 cases, 1 was consequent upon a wound of the pleura, 4 upon other foci of suppuration, and 2 upon bronchopneumonia. Rosenbach's 1 case followed a bullet wound. Of 3 cases observed by Huguenin, 1 followed a suppurative angina, and 2 were from anthrax. Of Netter's 6 cases one each followed ulcerative endocarditis, pyæmia, and aspiration; in the other 3 the cause was unknown.

In the mixed forms the staphylococcus plays a secondary rôle, and its associate nearly always determines the character of the suppuration.

The *Eberth bacillus* of typhoid fever has been found in empyema by Weintraud; also by Loriga and Pensuti. In both of these cases the bacillus was present in pure culture; one—Weintraud's—recovered without intervention, the other after operation. The serofibrinous form of pleurisy is much more common after typhoid than the purulent, the proportion in Ehrlich's six cases being five to one; in this one case the staphylococcus alone was found.

The *encapsulated bacillus of Friedländer* has been met with twice: once by Letulle, and once in pure culture by Netter.

Finally, the so-called *saprogenic microbes* are invariably found in all cases of *putrid empyema*. These germs are constantly present in the mouth and digestive tract; and Netter has succeeded in producing a putrid empyema by the introduction of saliva into the healthy pleural cavity. It may, therefore, be considered established that all cases of gangrenous pleurisy are produced by the invasion of these organisms. Netter cites the following varieties as present, being found either in pure culture or greatly predominating, in twenty cases of putrid empyema which he examined: The bacillus found by Löffler in diphtheria of the calf, the spirochæte denticola, the bacterium coli commune, and the leptothrix, besides also numerous other forms.

The *pathological conditions* in which such invasion is possible are mostly destructive or ulcerative processes in the lung or gastrointestinal canal. They either may give rise to a pleurisy which is putrid from the outset, or an existent serofibrinous or purulent effusion may subsequently become infected. Netter considers the former by far the more common. Such destructive processes are:

Pulmonary.—Most important among these is *pulmonary gangrene,*

especially the lighter forms of cortical gangrene, which not infrequently result from bronchopneumonia. Most putrid empyemas have this origin. Less frequent causes are *bronchiectasis*, which always contains these germs of decomposition; also *phthisical cavities*, *hydatids*, and *cancer*.

Gastrointestinal. — Among these may be mentioned *cancer* and *stricture* of the *œsophagus*; *retropharyngeal phlegmons*, which advance along the mediastinum; *abscesses* of the *abdominal cavity* or *viscera*; and *ulcer* or *cancer* of the *stomach*.

Often the original lesion cannot be determined, and it is probable that in the majority of such instances the air passages are the channels of invasion.

Such are the etiological factors now universally recognized as essential to the production of empyema. Without microbic invasion no form of pleural suppuration is possible. The relative frequency of the different varieties may be summed up as follows: *In adults*, 50 per cent. of all cases are streptococcal, 25 per cent. are pneumococcal, and the other 25 per cent. are divided among several forms, of which the tuberculous is relatively most common. *In children*, the pneumococcus causes at least 60 per cent., possibly 75 per cent., of all cases; most of the remainder are streptococcal or staphylococcal, both tuberculosis and putridity being rare.

Pathological Anatomy.

Purulent pleurisy may be such from the very outset, or, as is probably a much more common occurrence, an effusion which is at first serofibrinous gradually changes to pus. In reference to most of the pathological changes in empyema we have only to refer to what has been said on simple effusion. The early appearances in the pleura are the same, as are also the mechanical effect of the effusion upon the lung and neighboring organs. The depression of the diaphragm is, however, apt to be more pronounced in empyema; and it is here that the extreme cases, in which the diaphragm protrudes in the hypochondrium as a fluctuating tumor, are usually encountered. This is partly due to the greater weight of pus, and probably also in part to a greater degeneration of the diaphragmatic muscles; the same may be said of the intercostals, an early obliteration or protrusion of the intercostal spaces being much more common in empyema than in the serofibrinous form.

In most cases of empyema the pleural walls are covered to a varying depth with a fibrinous deposit. This may be yellowish or grayish-white, or, in putrid empyema, green or even brown. Sometimes

in fresh cases the pleuræ are found perfectly smooth and glistening, as if but little altered. In other cases of considerable duration the new membrane has a granulating surface, which may also be either clean or covered with false membrane.

In *tuberculous empyema* the pathological lesions vary with the duration of the process. Osler describes a rare form, of acute onset and course, in which a condition of extensive ulceration of the pleural walls may arise in the course of a very few weeks. Usually the process is extremely chronic. The pleura is then found greatly thickened, especially the parietal, where the lesions are usually most advanced. Its surface is uneven and presents numerous depressions, resembling ulcers partly filled with cheesy material. On section, the cut surface presents numerous small grayish or yellowish spots which prove to be tuberculous granulations. The whole pleural wall resembles that of a cold abscess.

In purulent pleurisy, especially, the lymphatics of the pleura are often found engorged with pus, as well also as those of the interlobular pulmonary septa. In this way the suppurative process may invade the lung, and the pus finally escape through a bronchus. More commonly, however, the mode of spontaneous evacuation is a different one. The pus exercises a sort of corroding action upon the pleura, usually in certain limited areas, involving either the costal or pulmonary layer. In the former case, there may be a resulting perforation of an intercostal space—the so-called "empyema necessitatis." Oftener it is the pulmonary pleura which is eroded, and the pus is then forced by the expiratory pressure of cough through the pulmonary alveoli into the bronchial tubes; while, owing to the very slight degree of inspiratory expansion, the air within the lung is unable, so to speak, to stem the tide of pus and gain entrance to the pleural cavity. This explanation of Traube is now generally admitted to account for the fact that the rupture of an empyema into the lung is not usually followed by pneumothorax.

In rare cases the suppurative lymphangitis above referred to may be so extensive that the whole lung is involved in a condition of purulent softening; the larger bronchi alone resist the suppurative process, and present a peculiar appearance as they float out into the surrounding pus.

Besides the lung and external chest wall, other organs may be invaded by the pus of an empyema. It may rupture into the œsophagus, or very rarely into the pericardium; or it may gain entrance to the mediastinum, and thence to the pleura of the opposite side. In other cases the pus finds its way through the diaphragm, either directly or along the psoas muscle. In the former event it may pro-

duce a subphrenic abscess, or open into the free abdominal cavity, or result in a large retroperitoneal abscess, as in a case observed by Leyden, in which the abscess eventually pointed at the umbilicus. Along the psoas the pus may sink to the loin, or to below Poupart's ligament, or may even, as reported in one case, appear in the popliteal space. All of these occurrences are especially rare at the present time, when most empyemas are recognized early and operated upon without delay.

The character of the pus in empyema is varied. In consistence it may be scarcely more than an opaque serum or so thick and viscid that it can hardly be poured from a glass. Very often its lower layers are thick and purulent, while above it is quite transparent. Its color may be creamy, or more grayish, or a light shade of green, or more or less pink or red from the presence of blood; if putrid, it may be a dirty brown. The odor is usually sweetish and not disagreeable, but in putrid cases it may be exceedingly offensive and so penetrating that a whole ward will soon become infested. Microscopically it contains, besides leucocytes, a varying number of red blood corpuscles, fatty degenerated epithelium, cholesterin crystals, and free fat globules; the latter may be present in great quantity, and produce the so-called chylous forms hereafter to be described. Eichhorst and Grawitz have both encountered Charcot's crystals, which resemble closely the spermatic crystals of Boettscher. Grawitz thinks their presence in effusion should always suggest the possibility of its connection with hydatids, in which these crystals have hitherto been most frequently found.

A very interesting problem connected with empyema is as to the origin of the pus. It is usually thought to be a simple emigration of white corpuscles from the pleural capillaries; but Fraentzel pertinently remarks that the quantity which may be very rapidly produced in the pleural cavity greatly exceeds the total number of leucocytes in the whole body. Fraentzel, therefore, adopts the theory of a rapid cell division in the exudate itself. Schleiffarth holds that the pus is due to a rapid breaking down—a "fonte purulente"—of the connective tissue of the deeper pleural layer. The question still remains undecided.

In empyema of long standing, certain changes take place in the ribs and in the general conformation of the thorax. Helferich finds that the ribs may become much thickened, especially in the axillary region, so as to present a triangular shape on cross section. Again, it is in these cases that extreme thoracic deformity is oftenest encountered; the ribs sink in to aid the mediastinum and diaphragm in filling the space formerly occupied by the lung. The pleura becomes

in time greatly thickened, and its cicatricial contraction also aids much in finally closing the suppurating cavity.

Symptoms.

Empyema may be of acute and violent onset; or it may be subacute, sometimes developing out of the serofibrinous form; or its course from the very beginning may be latent and chronic.

Acute empyema is occasionally primary, and may be purulent from the first; oftener it only appears to be primary because no recognizable affection has preceded. There is usually an initial rigor, with cough, dyspnœa, and pain in the side, as in the serofibrinous form. These symptoms, together with the fever, vary much in severity, and in perhaps the majority of cases—such, for example, as follow pneumonia—there is at first nothing to suggest that the effusion is purulent. A graver form has been described by Fraentzel as pleuritis acutissima, in which both rigor and pain are unusually severe, and pus gathers with great rapidity, so that early dyspnœa may be extreme. Constitutional symptoms are very prominent; the initial temperature continues high, repeated rigors are frequent, the tongue soon becomes brown and dry, and there is rapid loss of strength with emaciation. The sensorium is clouded, there is often delirium, and the whole condition is markedly typhoidal. In the more fulminant forms death may occur in the first week. These cases of pleuritis acutissima are rare.

The second or subacute form of empyema is more common. Some pain, dyspnœa, and cough call attention to the chest, if this has not already been done by the primary disease. Fever is moderate, and there is at the outset nothing to arouse suspicion of anything beyond the usual serofibrinous form. The behavior of the temperature first suggests the possibility of pus; instead of falling to normal at the end of a week or ten days, it persists, or it again begins to rise. The morning temperature may be nearly normal, but every evening it again reaches a height of 102–103° F., and soon a regular hectic becomes established, which differs materially from the slight fever with marked intermissions which may persist throughout the course of a simple serous effusion. Sometimes the evening exacerbation is ushered in with chills or chilly sensations, rarely with rigors. With the development of hectic fever, the general condition begins, as a rule, to present marked signs of septic absorption. The face becomes pale and often of a slightly puffy appearance. Night sweats are not infrequent. The appetite is lost and there are progressive emaciation and weakness. Dyspnœa often in-

creases out of proportion to the growth of the exudate, being largely due to the cardiac asthenia which is indicated by the rapid and feeble pulse. Not infrequently there is slight œdema about the ankles, and in the course of time the fingers may become decidedly clubbed.

At the present time these cases are usually recognized long before most of the above symptoms have appeared, and submitted to operation. If not, recovery is still possible by spontaneous evacuation, or, in the rarest of instances, by fatty degeneration and subsequent reabsorption of the pus. Evacuation may occur through the lungs—the so-called vomica—or through an intercostal space; or, less frequently, in other situations, such as the lumbar region or groin (see Pathology). Of these possibilities, vomica is the most common and also the most favorable. The pus may suddenly escape by the mouth in large quantity, or its entrance into the lung may be more gradual and it may be coughed up in smaller quantities, like phthisical sputum. Pneumothorax may follow the development of vomica, but this is not the rule. Evacuation through an intercostal space—usually called empyema necessitatis—is less frequent and less favorable. It occurs oftenest in the fifth space, just outside the nipple (Marshall), but it may select almost any region of the thorax. In children the second interspace in front is said to be common; and it has even occurred at the posterior base close to the spine. At first a slight bulging appears, which increases in size, fluctuates, but rarely pulsates, and finally, after becoming purple and glazed at the summit, opens and gives exit to a large quantity of pus. This may end in recovery, but usually drainage is imperfect, fever and emaciation continue, and eventually the patient succumbs to progressive exhaustion, the last stages being often attended with œdema of the lower extremities and sometimes with colliquative diarrhœa. The appearance of such a patient is very similar to that of a victim of pulmonary phthisis. If life is sufficiently prolonged, albuminuria and an enlarged liver may indicate the development of amyloid degeneration.

Finally, certain forms of empyema are wholly latent from the very onset. Those which are secondary to other grave affections, or occur in already debilitated subjects, need not here delay us. Of more importance are the latent forms occasionally met with after pneumonia, or even when the streptococcus proves to be the agent of infection. The only explanation of these exceptional cases is a presumable difference in the virulence of these microbes under varying conditions. The most characteristic form of chronic empyema is the tuberculous. A genuine tuberculous empyema, one dependent upon a tuberculosis of the pleura and not merely occurring in a tuberculous subject, is

quite likely to develop in such a way that for a long time the patient is unconscious of any thoracic disease. Fever may be insignificant or entirely wanting, and the general nutrition but little impaired. This form has been called "empyema benignum," and is not incompatible with a fair condition of health for many years; on the other hand, it is a form from which the patient rarely recovers and to which he eventually succumbs. It will be again referred to under the symptomatology of the special forms.

Physical Signs.

An empyema does not present, in general, any characteristic physical signs which distinguish it from the serofibrinous form. It gives rise to the same phenomena of auscultation and percussion, producing precisely the same curve of flatness and the same displacement of organs. It is only the whispered voice which, as was first pointed out by Baccelli, frequently differs in the two affections; in serofibrinous effusions it is often transmitted to the ear with a distinctness which is seldom found in empyema. The sign is not, however, constant.

Œdema of the chest wall is a more valuable index of pus. While it may also result from a simple serofibrinous pleurisy, such instances are sufficiently rare to give the sign a more or less pathognomonic character as evidence of empyema. It may either involve the whole affected side or be limited to a certain area, and it may vary much in degree. It is undoubtedly inflammatory in character, and is not to be confounded with the simple œdema often found, in cases of more or less general dropsy, on the side upon which the patient habitually lies. Unfortunately, this inflammatory œdema is of exceptional occurrence, and its absence has absolutely no diagnostic value.

Symptoms of Special Forms.

Streptococcus empyema is, perhaps, of all varieties the one which oftenest has an acute onset and course (Vignalo, Netter). It is then characterized, according to general observation, by a fever which presents great oscillations in its daily course. The constitutional condition is often typhoidal; there are rapid emaciation, a brown tongue, and a tendency to sopor and delirium; it is here that many of the cases already referred to as pleuritis acutissima belong. Still there is no constant type, and the course of the disease may be comparatively mild and accompanied by a continued fever, or it may be wholly latent. The form may be purulent from the beginning; more frequently it begins as a serofibrinous pleurisy, the effusion

of which gradually changes to pus. This purulent change may be observed in the product of successive exploratory punctures; the fluid may be at first simply opaque, then seropurulent, and finally purulent. The pus is of a yellowish color, and separates on standing into a layer of opaque serum above and a moderately deep purulent deposit below. This separation may also take place in the chest itself, and exploratory puncture may thus prove deceptive.

The Pneumococcus Form.—Whether secondary to pneumonia or an apparently primary affection, this form may vary greatly in the acuteness of its early manifestations. In the majority of cases—sixty-three per cent., according to Netter—its onset is attended with fever, pain in the side, dyspnœa, and possibly a chill. Certain cases are quite suggestive of pneumonia; an initial rigor is followed by cough, pain, dyspnœa, and even herpes, as in three primary cases observed by Washbourne and one by White. As a sequel of pneumonia, empyema is perhaps most apt to appear in the second month, with renewal of acute febrile symptoms after those of the primary affection have entirely disappeared. It may, however, begin during the height of the disease; or, according to Netter, its development may be indefinitely retarded. In still other instances of both primary and secondary forms, the purulent collection may develop absolutely without pain or any constitutional disturbance other than weakness and anæmia. Renvers reports two cases, in one of which an afebrile interval of seven days followed a pneumonia, and two days later a fully developed purulent effusion was discovered; in the second, a pneumonia was immediately followed by empyema, but for seventeen days the temperature remained normal. The form has, therefore, no typical course, and its recognition must not be allowed to depend on the degree of constitutional disturbance.

Pneumococcal empyema seems to be rarely accompanied by œdema of the affected side. On the other hand, spontaneous evacuation, by vomica or through an intercostal space, is relatively frequent. No less than forty-one per cent. of Netter's cases were evacuated by vomica; and the experience of Gerhardt, Maziotti, and others has been similar.

The most essential peculiarity of this form from a clinical point of view is the character of the pus. In the first place, it is rich in cellular elements, the pus *bonum et laudabile* of the older writers. It is also apt to be extremely viscid, so that it can be poured from a glass only with some difficulty. Finally, it often has a decidedly greenish tint, likened by Netter to that of *purée* of peas. However, all of these peculiarities may be lacking, and their diagnostic value is merely suggestive.

The extremely benignant character of this form of empyema, as first emphasized by Leyden in 1885, and later by Netter, will be frequently referred to under prognosis and treatment.

Tuberculous Empyema.—It is stated by Osler that there is a form of tuberculous empyema which is of very acute onset and course; such cases, usually fatal, are said to present most extensive ulceration throughout the whole pleural cavity. The form is admitted by Osler to be very rare.

The characteristic course of tuberculous empyema is chronic and almost wholly latent. It may, it is true, begin as a more or less acute serofibrinous pleurisy, but in many cases its development is unnoticed. The patient seeks advice if at all because of some weakness and loss of flesh, or perhaps on account of moderate dyspnœa. Fever may be insignificant or entirely lacking. According to Netter the lungs are not, as a rule, primarily involved; and the fact that the parietal pleura generally shows the most advanced tuberculous lesions also indicates that these empyemas are not usually of pulmonary origin. The subsequent course of these cases varies. In some, pulmonary tuberculosis soon follows with its usual termination; others gradually succumb to the constitutional effect of the pleural disease. It is, however, remarkable how slow this may be in some cases; such an empyema is not incompatible with a fair degree of health for even several years.

The pus of tuberculous empyema is like that of any cold abscess; it is thin, seropurulent, of a grayish tint rather than creamy, and on standing deposits a powdery sediment. It is not infrequently slightly hemorrhagic. Microscopically it is nearly always rich in fat globules, and these may at times be present in such quantity that the appearance of the fluid is distinctly chylous (see Chylous Pleurisy).

Putrid Empyema.—This form has no onset or course peculiar to itself. Often acute and even violent, it may, on the other hand, be of only moderate severity, or even quite latent. In the acute cases certain symptoms may be unusually prominent. Pain in the side is said to be often of very great severity and persistence. The temperature is apt to be high, and to show marked morning remissions. A general typhoid condition is a still more characteristic feature of some cases; the tongue soon becomes brown and fissured, the skin is hot and dry, the sensorium is clouded with a tendency to delirium, and the general nutrition becomes rapidly and seriously impaired. In the less acute forms there is, as a rule, nothing in the symptoms and course to suggest putridity. Sometimes the expectoration does become fetid even when there is as yet no communication

between the lung and the pleural cavity; if the latter occurs, the sputum will, of course, be considerable in quantity and intensely putrid. Pneumothorax is a not uncommon complication of putrid empyema, and may have been the primary affection.

The pus withdrawn on aspiration has sometimes the odor of animal decomposition, sometimes that of rotten eggs. Its color may present nothing peculiar, or it may be of varying shades of brown. The pus is by no means always thick and creamy; it tends rather to be of seropurulent consistence, and here also, as in the streptococcus form, there may be an intrapleural separation into a cloudy layer above and a purulent deposit below—a condition which might create some confusion on simple exploratory puncture.*

Varieties of Pleurisy.

Hemorrhagic Pleurisy.

The term hemorrhagic pleurisy is properly applied only to those cases in which the exudation contains a very considerable quantity of red blood corpuscles, and has a color varying from a decided pink or a cherry red to a reddish or even dark brown. Still, a smaller amount of blood is apparently not without significance. Grawitz, in 48 microscopical examinations of pleuritic effusions, found red blood corpuscles (quantity not stated) in only 10; 8 of these were in tuberculous subjects, 1 was in a case of leukæmia, and 1 in a case of pulmonary cancer. It would appear from these observations that the usual statement is not correct, according to which all serous effusions contain red blood corpuscles; and they would also suggest that the presence of blood, even microscopically, is strong evidence of tuberculosis. Dieulafoy has shown that five to six thousand red discs to the cubic millimetre must be present in order to impart the faintest rose color to an effusion.

Frankly hemorrhagic effusions may be met with in the following conditions:

Pleural and Pleuropulmonary Cancer.—Effusions from this cause

* In the foregoing description of the various etiological forms of empyema, I have followed very closely that of Netter. Such generalizations are possible only when the material at hand is large, and a bacteriological examination is made in every case; and up to the present time it seems that Netter alone has made a careful comparison, in a large series of cases, between the bacteriological and clinical features of empyema. While, therefore, the whole subject must still be regarded as in its primary stage, many of Netter's observations have been already confirmed; and I have considered them of sufficient practical value and suggestiveness to warrant an extended reproduction in this volume.

are hemorrhagic only when the process is more or less destructive. The quantity of blood is then likely to be very considerable, and it is here that the deeper tones of red are seen. The subject will again be referred to in the section on Malignant Growths.

Pleural Tuberculosis.—In this form the proportion of blood is generally much less, and the effusion is not, as a rule, deeply colored. It is hardly necessary to say that but a small proportion of pleurisies occurring in tuberculous individuals are hemorrhagic. It is probable that such is the case only when there are tuberculous lesions in the pleura itself. This tendency to hemorrhage is to be explained by the great vascularity of the new membranes, and the frequency of degeneration and necrosis of the arterial walls consequent upon the tuberculous process. Many of these hemorrhagic cases are acute—a miliary tuberculosis of the pleura, such as may occur *sub finem vitæ* in pulmonary tuberculosis or, less frequently, as a primary affection. Others are chronic from the first; beginning as an ordinary acute pleurisy, they show a constant tendency to recur. Such cases may recover after repeated tappings, but the probability of subsequent phthisis always makes the outlook especially dubious.

In this same group probably belong also those forms of hemorrhagic pleurisy which Fraentzel first described as analogous to Virchow's hæmatoma of the dura mater. Mesnil and Netter refer to this condition as pleural hæmatoma. An individual who has recently recovered from an ordinary serofibrinous pleurisy has a relapse; the new membranes which have resulted from the first attack participate in the recurrent inflammatory process, and very considerable quantities of blood escape from the newly formed capillaries, either by rupture or, as Fraentzel thinks, by diapedesis. This blood may collect in the meshes of the membrane, or in the free pleural cavity where it mingles with a variable quantity of serum. Fraentzel considered these recurrent forms of hemorrhagic pleurisy as almost invariably associated with pleural tuberculosis; Mesnil and Netter both coincide in this view. Indeed, Fraentzel believes that this is the mode of development of nearly all hemorrhagic effusions of tuberculous origin, except the more acute forms.

The hemorrhagic diathesis is not of itself a cause of pleurisy; but a pleural inflammation occurring in an individual thus predisposed is liable to be hemorrhagic. This form is rare. It may be encountered in connection with purpura hæmorrhagica, scorbutus, pernicious anæmia, leukæmia, hæmophilia, or icterus gravis. The loss of blood may be considerable—sufficient to cause a noticeable pallor. Instances have also been reported of the association of hemorrhagic effusion with chronic Bright's disease and with cirrhosis of the liver.

It is also probable that hemorrhagic pleurisy is occasionally independent of any of the foregoing conditions. Wentworth reports a case containing only the staphylococcus (possibly tuberculous [?]), and states that he has seen another which was quite similar.

The proportion of pure blood in a hemorrhagic pleurisy is rarely more than ten per cent. But it is often impossible to estimate this proportion either by the appearance of the fluid or by microscopic examination; many of the red discs have lost their color and are difficult to count. Henry recommends for this purpose the use of Gowers' hæmoglobinometer. In an anæmic and debilitated individual such an estimate may be of value as regards aspiration, since the recurrence of a markedly hemorrhagic effusion might then be attended with considerable danger.

Chylous Pleurisy.

Certain cases of effusion have been reported in which the fluid was of a decidedly milky appearance, resembling chyle. The form is very rare; Busey was able to collect only sixty-four cases in the whole literature of effusions. Following the example of Boulengier, who has given considerable study to the matter, we may divide chylous effusions into two distinct and sharply characterized forms:

Chylothorax.—A collection of true chyle in the pleural cavity can result only from a direct lesion of the thoracic duct. Of Busey's 64 cases, only 10 were genuine chylothorax; in 5, at least, of these, the chyle came directly from the thoracic duct, 3 being traumatic. In a case since observed by Turney, five ounces of chyle were present in the peritoneum, two pints of chyle in the right pleural cavity, and one pint of cloudy serum in the left. The thoracic duct was found to be obstructed by a thrombus of the subclavian and internal jugular veins, which had resulted from a cancerous embolus. Boulengier thinks this form may also be due to the operation of the filaria sanguinis. Microscopically the effusion in chylothorax is found to consist of a pure emulsion of fat.

Chyliform Pleurisy.—Here the fluid simply resembles chyle and has no relation whatever with any lesion of the thoracic duct. It is found in chronic cases of serofibrinous or purulent pleurisy, also in pleural cancer, and is due to a fatty degeneration of fibrin, leucocytes, or epithelial cells. Microscopically, it consists of a finely granular detritus, free fat globules, and numerous crystals of cholesterin, many of which are aggregated in clumps. Degenerated leucocytes and epithelial cells are present in small numbers. Both the granular detritus and free fat are more or less completely dissolved by ether.

A chyliform effusion is usually thought to be tuberculous. While the majority of such effusions are undoubtedly associated with the chronic forms of pleural tuberculosis, a very considerable number are the result of cancer. Quincke regards a chylous fluid as quite as characteristic of malignant disease of the pleura as a hemorrhagic one. Of twenty cases of chyliform pleurisy whose origin could be traced by Bargebuhr, four were associated with cancer. It need hardly be said that the prognosis of this form *quoad vitam* is always grave.

The diagnosis of either form of chylous effusion can be made only by exploratory puncture. A chyliform fluid may then, as Boulengier thinks, be distinguished from true chyle by its cellular elements which are usually present in sufficient numbers to make a diagnosis possible.

The treatment of chyliform pleurisy is the same as that of other forms of chronic empyema. The prognosis of true chylothorax must always be exceedingly grave, and it would probably be unwise to operate except in response to the *indicatio vitalis*.

Pulsating Pleurisy.

Under this term two conditions are usually included, which differ widely in appearance. In the first a pulsation, synchronous with the heart, is seen or felt in several intercostal spaces of the affected side. In the second the pulsation is limited to one or more tumors, each of which represents a beginning perforation of the chest wall.

The condition is extremely rare. Attention was first called to it by McDonnell in 1844; and it has since been studied among others by Comby in 1883, who collected twenty-seven cases; by Keppler in 1887, with thirty-eight cases; and by Osler, who in 1889 found a total of forty-two cases in the whole literature of the subject. With one or two exceptions, all the reported cases have been purulent.

This pulsation is found only when the empyema is upon the left side. Its most frequent situation is from the second to the sixth rib in front, outside the mammary line. This is true of both varieties. In other cases the pulsating area or tumor may be in the lower axillary region, or even at the lower part of the back, close to the spine (case of Millard). There may be two or even more separate pulsating tumors. Light reports two such cases; in the first, one tumor was over the third, fourth, and fifth ribs, near the mammary line, the other was below the angle of the scapula; both pulsated. In the second case, one bulging was in the præcordia, the other at the eighth rib in the axillary line; only the latter pulsated; these tumors were both red and glazed.

In some of these cases there is a pyopneumothorax. Indeed,

Comby is of the opinion that the great majority are thus complicated. In certain positions of the patient the tumor may then contain only air.

No satisfactory explanation of this phenomenon, accounting at the same time for its infrequency, has ever been given. The fact that the pulsation sometimes ceases after the removal of a small quantity of fluid by aspiration, suggests, as believed by Traube and Bouveret, that one of the necessary conditions is an unusual tension of the fluid, together with a locally diminished resistance of the thoracic wall. These cases are supposed to be unusually fatal, and to be very frequently tuberculous. They are certainly not always chronic, since Watkins has recently observed pulsation in an acute case. Of Light's three cases, one recovered, and in the other two no tubercles were discovered on post-mortem examination. The treatment of pulsatile empyema differs in no way from that of the ordinary form.

Encapsulated Pleurisy.

Either a serofibrinous or a purulent effusion may be variously limited in extent and configuration by old adhesions. We have already referred (see Pathological Anatomy) to the forms described as multilocular and areolar, where the fluid is contained either in several communicating chambers or in the meshes of the thickened pleura. Here vocal fremitus may be but little diminished; and on aspiration the quantity of fluid obtained may be disproportionately small. In other cases and more frequently, a single body of fluid collects in front, or at the apex, or above the diaphragm; in fact, in any possible region of the chest. This will result in atypical displacements of the lung, as, for example, downwards or outwards or forwards. Mohr found more or less encapsulation in more than half of forty-nine cases examined, though this is assuredly far beyond the usual proportion. These limited effusions often occasion great difficulty in diagnosis; they have been mistaken for consolidations, new growths, partial pneumothorax, and for pericarditis. It is impossible here to enumerate the varied physical signs which they may produce, and the elements of diagnosis presented in each case. Particular weight will be attached to the presence of absolute flatness, local bulging, cardiac displacement, the absence of fremitus, and a diminished or bronchial respiration without râles. The exploratory needle will always remain the final and only authoritative source of information.

Diaphragmatic Pleurisy.

This form, as its name implies, affects that portion of the pleura which covers the diaphragm and the corresponding surface of the lung. Its course and symptoms have not necessarily anything pecu-

liar. Such a pleurisy may often form part of a more general inflammation, or may be secondary to grave affections of the lungs or abdominal viscera, and thus present no local symptoms which attract attention; or even a primary diaphragmatic pleurisy—such as may result from rheumatism, for example—may run a chronic and latent course. In certain cases, however, this form gives rise to a characteristic complex of symptoms, which is especially interesting and important because of its close resemblance to serious disease of the abdominal cavity. First studied by Laennec, Andral, and later by Hermil and other French observers, such German authorities as Wintrich and Fraentzel have refused to recognize its *raison d'être;* the latter claiming that, on the one hand, it may produce no symptoms whatever, while other cases are not to be distinguished from certain affections of the lung and abdomen—as, for instance, subphrenic abscess. A brief *résumé* of four cases recently reported by Fenwick will perhaps aid in deciding as to which of these views is justified, as well as in emphasizing the peculiar symptomatology of the disease:

Case I. presented all the symptoms of an attack of gall stones, and was thus diagnosticated until the third day, when dulness appeared at the base of the right pleural cavity behind.

Case II.—Chill, pain in the right iliac fossa, retching, and slight delirium. Pulse, 120; respiration, 36; temperature, 102.6° F. Diagnosis, perityphlitis. On fifth day a friction sound was heard behind; later, effusion appeared.

Case III.—Acute abdominal pain, constant retching, temperature of 103° F. Six hours later the legs were drawn up, and there was constant vomiting; temperature, 104° F. Diagnosis, probable perforative peritonitis. Death thirty-six hours later (phthisis). Autopsy showed only a fresh deposit of lymph over the whole pleura covering the diaphragm on the left side and the opposite lung.

Case IV.—Sudden epigastric pain, with vomiting and delirium; knees drawn up, respiration rapid and shallow, abdomen retracted and rigid, with great tenderness on pressure. Diagnosis, probable peritonitis. In twenty-four hours amelioration of all general symptoms, with signs of beginning effusion, which afterward became large.

These cases suggest the symptomatology of acute diaphragmatic pleurisy: Acute onset, often with chill and high temperature; pain, frequently of great severity, referred to the epigastrium or hypochondrium, or even to the iliac region, sometimes also to the lower part of the back, and greatly aggravated by cough, deep inspiration, and hiccough—the latter often an early and prominent symptom; respiration moderately rapid and shallow, with bent posture; abdominal symptoms pronounced—legs often drawn up and abdomen exceedingly sensitive on pressure; general condition markedly disturbed—face anx-

ious, fear of impending death, pulse rapid, sensorium dulled, delirium not infrequent—all these symptoms subsiding in from one to four days, and giving place to those which commonly attend an ordinary serous effusion.

The physical signs are always slight at first and may remain so throughout. Probably in most cases there is either a serous or, rarely, purulent effusion, although here opinions differ, and since recovery is the rule the truth cannot always be determined. The earliest sign of any value is friction, and later a zone of dulness may appear behind, as in the usual form.

The cases of Fenwick also illustrate the great difficulty of diagnosis at an early period. Everything points to an abdominal disease, and a recognition of the true nature of the malady is only possible when the possibility of a pleuritic affection is kept constantly in mind. The differential factors are the following: In pleurisy the abdominal tenderness is superficial, being due, according to Fenwick, to irritation of the intercostal nerves, whose branches are distributed to the abdominal wall. Respiration is increased in a degree unusual in abdominal affections. Certain points of tenderness along the course of the phrenic nerve are often marked and characteristic. These are: Between the insertions of the sternomastoid muscle, in the intercostal spaces along the sternal margin, over the diaphragmatic attachments, especially close to the spine, and at a point on a level with the tenth rib and two fingers' breadth from the median line. Later, the amelioration of the general condition and the appearance possibly of local physical signs reveal the true nature of the disease.

The prognosis and treatment of diaphragmatic pleurisy present no special features for consideration.

Interlobar Pleurisy.

This form is nearly always purulent. Attended at the outset by the usual symptoms of pleurisy, it may fail to produce any physical signs whatever and, unless emptied by vomica, it may remain unrecognized.

In other cases the effusion finally reaches the surface of the chest, or, rather, it gives rise to a dull area which may represent either the fluid itself or only a thickening of the surrounding lung. This dull area has no especially diagnostic features. It does, however, usually lie in the course of a pulmonary fissure—a fact which may possibly suggest its character. Gerhardt, for example, reports a case which produced an area of flatness with bronchial respiration in the right axilla, and which emptied itself by vomica on the nineteenth

day. Netter also states that a flat area is often produced, which extends from behind forwards and downwards, corresponding to the fissure between upper and lower lobe.

Mediastinal Pleurisy.

A pleurisy affecting the mediastinum alone is exceedingly uncommon; it is usually only part of the more general affection. But such cases have been reported; purulent collections have been found, usually in the anterior mediastinum, which during life produced considerable pain and dyspnœa, and sometimes a small region of dulness to the right or left of the sternum.

Velinurovitch observed three cases in children, the signs of which were more interesting and characteristic. Circulatory disturbances were very pronounced; there were cyanosis, rapid and feeble pulse, œdema of the face and upper portions of the body, and coldness of the extremities. Physical examination showed dilatation of the sternal veins; also an area of flatness which extended slightly beyond the sternum on the unaffected side, and on the other for a varying distance towards the axilla. This area was continuous with the dulness of the heart and liver, the former being displaced towards the opposite side.

Velinurovitch thinks the greatest difficulty in the diagnosis of this condition is its differentiation from pericardial effusion. It would seem as though the characteristic area of flatness produced by the latter would usually make confusion impossible.

Double Pleurisy.

It is seldom that both pleuræ are simultaneously attacked by an acute inflammation, and still rarer for both at the same time to become more or less filled with fluid. A bilateral collection of serum is far more likely to be a simple hydrothorax.

Double empyema does, however, occur, especially in children. The symptoms are apt to be severe, and it is quite evident that a bilateral compression of the lungs and circulatory organs must be attended with great danger. It was formerly believed that double pleurisy is invariably tuberculous. This is probably not far from the truth as regards the serofibrinous form, although Netter refers to such cases of rheumatic origin. As to the tuberculous character of all double empyemas, there is very great doubt; at all events, quite a number of instances have recently been reported by Carr, Cassel, Dunn, Westbrook, Batchelor, and others, in which operation of a double empyema was followed by complete recovery. Batten even had five recoveries out of eight cases in children.

The treatment of this form presents no special feature, except that an interval of several days should elapse between the two operations.

Pleurisy in Infancy and Childhood.

It is now generally admitted that pleurisy in children is comparatively common. It may be either dry, serofibrinous, or purulent; the latter is, perhaps, the most frequent form. Even infants are not exempt, though more so than older children; and, according to Rotch, the younger the child the more likely is the effusion to be purulent.

Serofibrinous Pleurisy.—No careful study of the etiology of this form in childhood has yet been made. It seems quite improbable that it can bear any such close relation to tuberculosis as that in adult life. Still, it is often apparently primary, and whether such cases are frequently rheumatic or are often dependent upon one or the other of the various microbes, is still undetermined. Henoch states that he has frequently seen it in the course of acute articular rheumatism.

The disease may begin with violence, and its course may be even more acute than in adults. At the outset convulsions are not infrequent. Baginsky emphasizes especially the constancy of a short, dry, harassing cough. Infants cannot, of course, call attention to pain; but there is often great intercostal tenderness on percussion or palpation over the affected region, or even on merely pressing the skin. Somewhat older children are very apt to complain of the "stomach." Fever is usually high, often over 104° F., and greatly adds to the dyspnœa, which is so often produced in children by high temperature alone. Delirium is also of common occurrence. Some cases, beginning like pneumonia with repeated convulsions, may strongly suggest meningitis. In others gastric symptoms predominate—such as anorexia, nausea and vomiting, and epigastric pain. The advice given by Henoch, to examine the chest of every child with fever, is sound. The pulse is not so much affected by an increasingly large effusion as in adults. Baginsky says the right heart in childhood is relatively large and strong, and is therefore better able to overcome and adapt itself to any obstruction in the lesser circulation. In older children the course of serofibrinous pleurisy is, as a rule, not so acute, and corresponds more nearly to the adult form.

Particular attention should be called to the relative frequency of latent pleurisy in childhood. The importance of this form in infants and younger children is all the greater because of their inability to speak of the fleeting pains or other symptoms which might direct attention to the chest. Such a pleurisy may be absolutely latent. Only an increasing pallor and weakness, with perhaps some

loss of flesh, finally lead the parents to consult a physician. His recognition of the disease will then depend solely upon the habit of making a thorough physical examination in all cases in which the diagnosis is not clear.

The physical signs of pleurisy in childhood differ but little from those in adults. Friction is said to be much softer. Bulging of the intercostals is much more frequent and pronounced. Bronchial respiration over the fluid is of very common occurrence even in small effusions. Henoch regards it as the rule. Fremitus is commonly said to be of little value because it is difficult to elicit; in my experience it is very seldom that a child cannot be made to use the voice in one way or another. Percussion curves are the same as in later years; and, owing to the great ease with which the flat area can be defined in childhood, their diagnostic value is very great.

Serofibrinous pleurisy in children is a relatively benign disease. Metabolism is more active in early life, and resorption of an effusion is usually rapid and complete. Chronic cases are occasionally met with, and may have the same outcome as in adults. Complications are few. Of these, pericarditis is relatively frequent, and must always be looked upon with considerable apprehension. Sudden death is rare.

Empyema in childhood has already been referred to in the section on Etiology. The great frequency of the pneumococcal form, constituting probably seventy-five per cent. of all cases, was particularly emphasized. This explains also the well-known benignity of empyema in children, the pneumococcus being a microbe of slight virulence and short life. Other important etiological factors are the acute infectious diseases, particularly scarlatina; bronchopneumonia of streptococcal origin, especially when associated with influenza; and also caries of the ribs, which, according to Henoch, is a much more frequent cause than in adults. Putridity is rare. Resulting deformity of the chest is comparatively infrequent in childhood; and it is the experience of most operators that a complete restoration of normal conditions is the rule.

The treatment of simple effusion is the same as in adult life, and that of empyema is fully discussed elsewhere.

Senile Pleurisy.

Here also the disease, while occasionally acute, is oftener subacute or latent. This is what the debility of age would lead us to expect. Netter states that senile pleurisy is very rare apart from pneumonia, tuberculosis, cancer—especially of the lung—chronic Bright's disease, and pulmonary infarction, such as results from dis-

ease of the heart. Its course is rather protracted, the amount of fluid is usually small, and the ultimate outcome is always doubtful, because of the usually grave character of the primary disease.

Complications of Pleurisy.

It is unnecessary and impossible here to enumerate the many conditions with which pleurisy may be associated (see Etiology). Genuine complications of pleurisy, such as more or less habitually result from it, are few.

Pericarditis is perhaps the most frequent complication. It may follow either the simple or the purulent form; and it may either be dependent upon the same cause as the pleurisy itself—such, for example, as rheumatism—or it may result from a direct extension of the inflammatory process. It is oftenest, perhaps, accompanied by pericardial effusion, which may or may not be of the same character as the pleural. The diagnosis, in connection with a small pleuritic effusion, is easy; with a large effusion, especially if on the left side, it can be made only by careful percussion of the displaced præcordia, which then reaches much above the fourth costal cartilage on the right—its usual boundary. Pericarditis is always a grave complication; not that recovery is exceptional, but that the possibilities of a fatal outcome are materially increased. A heart which is already overworked and in some danger from compression, can ill afford to be additionally hampered by a pericardial effusion, and possibly also degeneration of its muscular substance.

Peritonitis is also a possible complication of pleurisy, especially of the purulent form; but, fortunately, even here it is rare. The diaphragmatic stomata are undoubtedly the channels of the inflammatory process.

Various *metastatic abscesses* have been found in connection with empyema. Those of the brain seem to be relatively frequent. Among a series of metastases from empyema collected by Hagenbach-Burckardt, were otitis media, abscesses of the scalp, gluteal region, and lids, and phlegmon of the cervical glands.

Pulmonary œdema is an occasional result of effusion, and may have a rapidly fatal issue. It may involve either the lung of the unaffected side or the one which has been compressed. Instances of the latter are found only when fluid has been too rapidly or copiously withdrawn by aspiration. The sudden refilling of the pulmonary capillaries appears to be the essential feature of the process, and it seems a matter of little importance whether, with Traube and Fraentzel, the escape of serum is attributed to a malnutrition of the com-

pressed capillary walls, or whether we accept the explanation of Duffin that a paralysis of the vasomotor nerves has resulted from long compression.

Œdema of the opposite lung is, Fraentzel states, of quite frequent occurrence at the height of a large effusion. No good explanation of its sudden onset has yet been given. Traube called it a pneumonia serosa, and thought it was associated with cold. A passive hyperæmia of the lung would seem to be a more plausible conception, though why it should appear so suddenly is not clear. The symptoms of œdema are often exceedingly acute and threatening. The patient is suddenly seized with a sensation of great pressure on the chest. Dyspnœa rapidly develops, which soon increases to orthopnœa, and is accompanied by cyanosis. At the same time a paroxysmal cough appears, which brings up large quantities of clear frothy serum, of yellowish or rose-red color, and very rich in albumin; hence the term "*expectoration albumineuse*," usually applied to this condition by the French. More than a litre may be raised in twenty-four hours. Death may ensue in a very short time from suffocation—a genuine asphyxia; or the symptoms may gradually subside, and in from twelve to twenty-four hours the *status quo ante* is again restored.

Œdema of the lungs has become comparatively rare as a complication of effusion, since early aspiration is the rule, and only a limited quantity of fluid is cautiously withdrawn.

Most prominent, perhaps, among the complications of pleurisy are certain peculiar *cerebral disorders*, and also certain forms of *sudden death*, which from their exceptional character may properly be considered here rather than among the more usual terminations of the affection.

Encephalic Disturbances.—Originally described among others by Weil, Rendu, Hutinel, and Gilbert and Roger, these attacks have recently been carefully studied by Cerenville, and especially by Jeanselme. Adopting the classification of the latter, we may recognize the following forms:

a. The Collapse Form.—This form occurs, as a rule, immediately after some operative procedure or manipulation, such as is frequent in cases of empyema; the patient becomes suddenly unconscious and dies of cardiac paralysis. Sometimes death is preceded by convulsive twitchings.

b. The Convulsive Form.—This is usually later in its appearance, occurring oftenest some time during convalescence. The patient is suddenly seized with convulsions, becomes unconscious, and goes through an attack which differs in no respect from one of epilepsy. The contractions are often unilateral, usually on the side of the em-

pyema. Death may occur during the seizure, or after a few moments the convulsions cease and consciousness slowly returns. The attack may be followed by paresis or paralysis, sometimes also by hallucinations or even mania. This condition is often termed "pleural epilepsy."

c. The Hemiplegic Form.—In this there occurs an onset of sudden paralysis which may or may not have been preceded by convulsions or unconsciousness. It may not follow the presumable cause for several days.

All these peculiar attacks appear to have this one element in common—they are invariably preceded by some mechanical insult to the pleura, however trivial in many cases this may seem to have been. Thus the attack may follow paracentesis, or the probing of a fistula, or, more frequently, a simple irrigation of the pleural cavity with a non-medicated fluid. In some cases, according to Cerenville, certain premonitory symptoms have been noticed—dilatation of one pupil, redness of the malar bone on the same side, and bleeding or hyperæsthesia of the pleural fistula. No satisfactory theory to account for these attacks has ever been offered. They are neither more frequent in epileptics nor does epilepsy afterward develop in those who recover. A long interval may, however, elapse between the manipulation and the seizure. Thus, Talamon saw a case of an eclamptic attack which occurred two days after an aspiration; three weeks later, without repetition of the puncture, there was a second attack which proved fatal. In one or two cases a cerebral embolus has been discovered; but for the great majority the unsatisfactory term "reflex" must still be used. Jeanselme assumes an increased irritability of the nerve centres from asthenia together with a certain degree of autointoxication. Gilbert and Roger have succeeded in producing convulsive seizures resembling pleural epilepsy by the injection of irritating substances into the pleuræ of dogs; and by vivisection they claim to have shown that these attacks were of reflex origin in the medulla.

This complication is rare. Jeanselme could collect but forty-five cases, to which at least two may now be added (Eisenlohr and Laache). All forms are extremely dangerous, the mortality being thus far no less than fifty per cent.

Sudden Death.—Though not a common accident in the course of pleuritic effusion, sudden death has been frequent enough to have given rise to much speculation as to its cause. Trousseau believed that a fatal syncope might result from a twisting of the great vessels, particularly the aorta, produced by displacement. Bartels laid chief stress upon a bending of the inferior vena cava where it penetrates

the diaphragm, sufficient to obstruct the return of blood to the right ventricle; this, combined with other factors, would greatly diminish the volume of blood in the left ventricle and cause a fatal insufficiency of arterial pressure. Fraentzel states that he has seen instances of this obstruction of the vena cava in three autopsies, and is therefore inclined to accept the explanation of Bartels for many cases in which the effusion is on the left side. Dieulafoy has, however, shown that sudden death is not confined to left-sided effusion. On the contrary, in a collected series of forty cases he found that in two-thirds the effusion was on the right. Other causes must therefore be invoked. Garland thinks there is often a fatal pressure upon the right auricle; and Fraentzel also agrees with Lichtheim that a sudden compression of the heart, such as may occur in a rapidly formed effusion before the heart has had time to adapt itself to the new conditions, may be a cause of death. Other cases may depend upon a fatty degeneration of the heart or other alterations of the myocardium caused by pressure (Raynaud, Sée, Comby). Pericarditis may be an important factor in producing the same effect. The majority of cases, according to French observers (Blachez, Négrier, Netter), result from thrombosis of the right heart and pulmonary artery, or from an embolus of the latter detached from a cardiac thrombus. "The patient is suddenly seized with great anxiety, extreme dyspnœa, and a sharp epigastric pain; the body is covered with sweat, the pulse is small and irregular, the heart sounds are indistinct and tumultuous; the voice becomes feeble; the patient casts a frightened glance about him, clutches desperately at the bed clothes, and falls dead upon the pillow. The whole scene has lasted ten minutes at the most" (Blachez).

Rarely, sudden death has resulted from aspiration. In some of these instances the shock of puncture alone has undoubtedly been sufficient to cause a fatal syncope in an already damaged heart; I know personally of such a case in which death followed a simple exploratory puncture. In other cases it may be that the theory of Hagen-Torn is correct—increased negative pressure in the thorax from aspiration, with consequent overfilling and paralysis of the right heart.

Sudden death, apart from instances due to aspiration, is an accident which occurs only in the more acute forms of pleurisy.

Sequelæ of Pleurisy.

These may be considered in the three following groups:

Tuberculosis of Other Organs.—We have already seen with what frequency serofibrinous pleurisy is followed by some form of tuber-

culosis, usually pulmonary. It is, however, to be questioned whether phthisis, for example, is to be regarded as in any true sense a sequel of pleurisy. It is quite possible, as we have shown, that the latter may be simply an early manifestation of infection. At all events, it is unnecessary to repeat what has already been said as to the relation between these two diseases.

Pleural Thickening and Adhesions.—A large proportion of all cases of pleurisy, of whatever form, have no local consequences other than the production of adhesions between the opposite pleural surfaces. These adhesions vary greatly in extent, but are rarely sufficient to impair seriously the functional activity of the lung. They consist of delicate cicatricial bands and cords, which, once formed, are usually definite, and remain unaltered through life. A diminished inspiratory expansion of the pulmonary margin is the only evidence of their presence. Possibly, when the pleural synechia is universal, the bronchi are less able to empty themselves than under normal conditions; and there may be therefore a greater tendency to inveterate bronchial catarrhs and disturbances of the pulmonary circulation. When the great frequency of pleural adhesions is considered (eighty per cent. of all individuals—Smith), it seems very doubtful whether these alone are often responsible for any serious impairment of the general health.

But in a few cases of both dry and serofibrinous pleurisy, and still oftener in empyema, much more is left behind than simple adhesions. Either as a result of recurrent inflammation or because the pleurisy is in its very nature proliferative, the pleura undergoes a gradual process of thickening. In serofibrinous pleurisy and empyema we often look for this result; the original inflammatory process never subsides, or there is constant recurrence, and the case from the outset is evidently chronic, and probably tuberculous.

It is otherwise in the dry form. Sir Andrew Clark has called especial attention to certain proliferate forms of primary dry pleurisy which are fraught with the most serious consequences as regards the subsequent health of the patient. An individual has an apparently insignificant attack of dry pleurisy. He rapidly recovers, and for a long time, years it may be, no effects of the pleurisy are visible. His health remains excellent; he suffers at most from some cough and tendency to bronchitis, or there may be occasional fleeting pains in the side. In time, however, his breathing begins to be slightly affected and he has some dyspnœa on exertion. His cough now develops a paroxysmal character, and the accompanying expectoration is hard to raise. Later this bronchial insufficiency is attended by more or less septic absorption, and the general health begins to fail. He

becomes especially liable to gastric and intestinal catarrhs. Finally albuminuria appears, the condition of the kidneys is from now on progressively aggravated, and eventually ends life. The duration of this process may have been ten or twenty years, or even more.

Clark made a very careful study of the pathological changes in these cases. He found the primary condition to be an excessive thickening of the adherent pleuræ, usually unilateral, and without any appearances suggestive of tubercle. In some instances this thickening amounted in places to one and one-half inches. The particular feature of the process was, however, the condition of the lung. Bands of connective tissue extended from the pleura for a varying depth into the pulmonary parenchyma, sometimes along the interlobular septa, sometimes along the bronchi, again following the course of the vessels. The fibroid process was most marked at the periphery, thus indicating its pleural origin. In extreme cases the whole lung was a mass of dense fibroid tissue. Often there was a secondary dilatation of the bronchi, a bronchiectasis; or, again, there were numerous cavities, which Clark considered necrotic and a consequence of fibroid occlusion of the terminal vessels.

Undoubtedly, most of these cases of primary pleuritis vegetans are tuberculous. The thickened pleura is then found on section to consist of diffuse tuberculous tissue, partly fibroid and partly caseous. In the earlier stages grayish or grayish-yellow tuberculous nodules may still be seen. It is the same condition which in other cases is attended by a serofibrinous or purulent effusion, and the lung may or may not be invaded by the fibroid process. The interesting question which Clark has raised is as to whether such chronic thickening and pulmonary involvement may occasionally develop quite independently of tuberculosis. Clark's observations would seem to answer this in the affirmative, but it must be regarded as still *sub judice*.

The *physical signs* of chronic proliferative pleurisy are much the same, whether it result from simple dry pleurisy, as Clark maintained, or from a serous or purulent form. Cicatricial contraction of the newly formed connective tissue in pleuræ and lung results in great deformity of the chest and more or less typical displacement of organs. The affected side is seen on inspection to be much smaller than the opposite; it appears sunken and depressed; the shoulder droops, the lower angle of the scapula tilts slightly outwards, and there is a lateral curvature of the spine—usually with its convexity towards the sound side. The lower margin of the ribs is nearer the crest of the ilium, and the ribs are closer together, so that the intercostal spaces are narrowed.

On percussion and auscultation the signs obtained are very simi-

lar to those of a moderate effusion. The lower half of the chest, at least, is quite flat, and the upper border of the flat area may resemble very closely that of a moderate effusion. Respiration below is much diminished or absent, and the voice sounds are distant and perhaps slightly bronchial. Pleural rustlings, creakings, and cracklings (Clark) are often abundant over the whole side; they bear a close resemblance to pulmonary râles, but are more superficial and are unaffected by cough.

I confess to having been for a long time very sceptical as to the real origin of such sounds in the pleura; but I now believe this to be comparatively frequent. I have at this moment a case under observation in which the crackling to-and-fro sound heard with moderate breathing becomes an unmistakable grazing friction at the end of deep inspiration.

Vocal fremitus is said by Fraentzel to be unaffected by pleural thickening; by Clark, Netter, and others to be much diminished. In my own experience it has varied in different cases, and I cannot think that it has any great diagnostic value. The heart may be variously fixed by adhesions; usually it is drawn towards the affected side. The diaphragm is raised, as may sometimes be recognized by widening of Traube's space. Over the upper half of the chest the signs vary so greatly, according to the condition of the upper lobe of the lung, that it is impossible here to attempt their description.

To distinguish this condition from effusion is often very difficult. Usually, of course, the past history, the sunken appearance of the chest, and the displacement of organs towards rather than away from the affected side, will establish the diagnosis. When, however, there are at the same time some signs of fresh pleurisy, such as pain and daily hectic, it may often be impossible to decide as to the presence of fluid, without exploratory puncture.

Even puncture may fail. I have within the past month operated upon a case of empyema in which for three years the signs of old pleural thickening and retraction had remained unchanged. The subject was tuberculous, and four months ago began to have a daily hectic. In great doubt as to the cause of fever—whether pleural or pulmonary inflammation—I made at different times six exploratory punctures over the flat area, with negative result. It was only when the patient was *in extremis* that a new zone of flatness appeared just above the liver in front, and a seventh puncture gave exit to pus. Resection and drainage are now resulting in speedy recovery.

The eventual outcome of chronic pleurisy and fibroid lung is always fatal. Pulmonary tuberculosis, if not already developed, must be regarded as constantly threatening. If this is escaped and life

is sufficiently prolonged, the patient will in most cases eventually succumb to chronic Bright's disease or to slow sepsis or to a dilatation of the right ventricle.

Amyloid Degeneration.—Long continued suppuration of the pleura not infrequently results in amyloid degeneration of the liver, spleen, kidneys, and other viscera. This condition is oftenest consequent upon old fistulæ, and is then to be regarded as one of the dangers which constantly threaten life.

Diagnosis of Pleurisy.

Friction is an absolutely pathognomonic sign of *dry pleurisy.* Since there is no sound more characteristic and easily recognized than friction, and since this sign is very constant, it follows that the diagnosis of dry pleurisy is, in the great majority of cases, extremely easy. Rarely friction is not produced; or, if present, it cannot be heard because of its situation (interlobar, diaphragmatic). A positive diagnosis then becomes impossible. In a previously healthy individual a sudden pain in the chest, which is aggravated by deep inspiration and attended by fever, is probably pleuritic. Intercostal neuralgia and pleurodynia are afebrile affections; they may, however, occur in a person who already has fever—as, for example, in phthisis—and then there will be considerable uncertainty.

Serofibrinous pleurisy cannot be distinguished from the dry form until signs of effusion actually appear. This might be anticipated when it is considered that there is probably no essential etiological difference between the two forms. In general, effusion is the severer affection, and its onset is more violent. Fever is more apt to remain continuously high from the start, whereas in dry pleurisy it usually falls after twenty-four to forty-eight hours.

At a very early period acute pleurisy may closely resemble pneumonia. The absence of rigor is a valuable criterion. In pleurisy friction is generally pronounced from the onset. In pneumonia the early signs are pulmonary, and friction appears later, if at all. Pneumonia causes a dyspnœa, which is more genuine and profound; it has not the same jerky and superficial character as in pleurisy, and it gives rise to greater cyanosis. After one or two days the physical signs of pneumonia become sufficiently characteristic. Diaphragmatic pleurisy may at the outset closely simulate an acute abdominal affection. Attention has already been called in the description of this form to the points of differential diagnosis.

The onset of *purulent pleurisy* may be suspected if the initial rigor is severe; if one of the common causes of empyema, such as pneu-

monia or scarlet fever, has preceded; if the pleuritic pain is unusually severe and prolonged; if a high initial temperature—of 104° F. or more—is maintained from the outset, with perhaps recurrent chills; and, especially, if there is rapid development of the typhoid condition, with delirium, brown tongue, and great prostration. In the great majority of cases the onset is not so violent and there is nothing to suggest suppuration.

The *diagnosis of effusion* must depend almost entirely on the physical signs caused by the presence of fluid. It cannot, therefore, be made until from two to five days have elapsed since the initial pain, and then only if the quantity of fluid exceeds at least half a pint, and is not so confined by adhesions that it cannot reach the surface of the chest.

There is no pathognomonic sign of a pleuritic effusion; and yet there is no condition of which the diagnosis can be made with so much certainty by the simple methods of physical examination. This certainly is possible whenever there is a combination of the following signs: 1. An area of flatness, which has a certain definite form; 2. Absent or diminished or bronchial respiration, without râles, over this flat area; 3. Diminished vocal fremitus.

The shape of the area of flatness on percussion varies, as we have seen, according to the quantity of fluid. It is, however, characteristic in each of its three forms, and its upper boundary will be found to present the following curves: 1. In small effusion the "convex curve," which is highest at the spine; 2. In moderate effusion the "letter of S curve," highest in the axilla; 3. In large effusion a curve with upward concavity which intersects the clavicle. In small and moderate effusions the diagnostic importance of these curves cannot be overestimated. It would, of course, be futile to attempt to estimate the exact relative value of each of the various signs in the diagnosis of pleurisy. In most cases one confirms the other, and we depend upon the sum total of evidence in reaching a conclusion. But it is just because so little is said by most authors in regard to these curves, that I wish to bring this point into strong relief. Flatness may result from numerous other conditions, such as cancer, hydatids, and fibroid phthisis. The same is true of the various auscultatory signs—none of them is constant, and none peculiar to effusion. Fine moist râles may be heard clear to the base of the chest. Vocal fremitus is, it is true, almost invariably absent over fluid, and is certainly a sign of extreme value; but it may be present in effusion, and absent over a consolidated lung if the bronchi chance to be occluded. On the other hand, the effusion curve is a sign which comes very near being pathognomonic. In an overwhelming ma-

jority of cases it means either an effusion or the fibrinous deposit or pleural thickening which an effusion has left behind. It cannot, of course, be denied that consolidation might possibly produce a dull area of similar contour; but a long series of cases has shown me that this must be an exceedingly rare occurrence. I would insist particularly upon the constancy of the curve which I have described as the "convex," and upon the ease with which by its aid these small effusions may be recognized.

The diagnosis of large effusion is so easy that it needs no discussion. The combination of flatness on percussion, involving a whole side, with marked displacement of the heart and diaphragm, can hardly suggest anything but fluid.

The affections with which the more moderate effusions are liable to be confounded are:

Pneumonia.—Flatness instead of dulness, voice and respiration diminished instead of increased or bronchial, fremitus also diminished or quite absent, no râles—these are the signs usually given as indicating effusion rather than consolidation. A loud bronchial respiration with bronchophony may be heard over an effusion; and if the latter happens to be of moderate size, the resemblance to a consolidated lower lobe will be very great; but percussion will almost invariably decide the question. In pneumonia the dull area is bounded above by the interlobar fissure—a line extending from the third dorsal vertebra outwards and downwards to the base near the mammary line. It is therefore highest at the spine; whereas, as we have seen, a moderate effusion is lowest at the spine and highest at the axilla. A sharper contrast could hardly be presented.

Pericardial effusion, when enormous, is said to have been often mistaken for a pleural. Such instances are difficult to comprehend. A pericardial effusion, however large, still retains its peculiar shape, and produces a perfectly characteristic area of præcordial flatness which a pleural effusion could scarcely simulate.

An *upward displacement of the liver*, or a *subphrenic abscess*, may produce a zone of flatness at the base of the chest, which may reach as high as the fourth rib in front, and behind present an upper level which is several inches above the base of the opposite lung. But the characteristic feature of upward displacement of the diaphragm is precisely this upper *level;* the upper border of effusion is never level, that of displacement is invariably so.

Tumors of the liver, growing from its convexity, may simulate effusion; but, aside from other more or less suggestive abdominal symptoms, the area of flatness produced by such tumors would rarely resemble the line of a typical effusion. The line of hepatic flatness

presents an irregular bulging, which may be in front, behind, or in the axilla. In a case of large central abscess of the liver, I found, for example, the upper border of the liver at the fourth rib in front, but in about the normal situation behind.

Is it possible to determine the character of a pleurisy from an etiological standpoint? Can we, for example, decide whether or not it is tuberculous? Unfortunately, not with certainty, though data upon which we may base a diagnosis are not, as a rule, entirely lacking. Tuberculous pleurisy is, in a certain degree, probable under the following conditions: A tuberculous ancestry—not, however, important evidence; signs of pulmonary tuberculosis in the affected individual; enlarged axillary or cervical glands; latent character of the effusion and tendency to chronicity, as shown by repeated recurrence after puncture; sterile character of the aspirated fluid, unless, as rarely happens, it is found to contain tubercle bacilli on microscopical examination, or tuberculosis is demonstrated by inoculation. If the pneumococcus is responsible for the pleurisy, this microbe is usually present in the fluid, and can be recognized under the microscope or by culture. The same is true of the Eberth bacillus of typhoid. Rheumatic effusions appear to have received hitherto but little attention. I can find no special observations as to their bacteriological character.

The amount of fluid can be only approximately estimated. The very discovery of effusion presupposes, as we have seen, the presence of at least a pint. Weil concludes from experiments upon animals that a normal adult pleura will hold about five pints of fluid at the moment of complete retraction of the lung, as determined by the appearance of high-pitched tympany in front. A further increase can only be estimated from the degree of displacement. Gerhardt states that twenty pints have been found in a single pleural cavity.

The diagnosis of *empyema*, as distinguished from simple or hemorrhagic effusion, can be made only by exploratory puncture. All other signs are inconstant and often misleading. Local œdema is found in only a small minority of cases, valuable as it is when present. It is extremely unwise to depend upon the development of a hectic fever with marked oscillations; for, on the one hand, constant fever is common enough in serofibrinous pleurisy, and on the other, an empyema may produce only the most trivial rise of temperature. Repeated rigors in empyema are very rare. Clubbing of the fingers and œdema of the lower extremities are, when present, fairly good signs of pus; they are not frequent, and are of late appearance. In short, there is, in a very great majority of cases, the utmost difficulty in deciding as to the character of an effusion without exploratory puncture.

Exploratory Puncture.—As far as I am aware, there is absolutely no contraindication to the use of this means of diagnosis. The pain is trivial; and by the preliminary injection of a few drops of a one-per-cent. solution of cocaine, as is often advisable in children, it may be entirely avoided. The objection that it may transform a serofibrinous into a purulent exudate is now rarely heard, for it is now recognized that this change often occurs where there is no interference whatever, and, furthermore, all danger may be avoided by the use of a needle which has been thoroughly boiled.

An excellent method of disinfecting an ordinary hypodermic syringe has recently been suggested by Hofmeister, and successfully used by Powers. The leather washers and plunger are first soaked for twenty-four hours in a four-per-cent. solution of formalin. The syringe is then put together, filled with water so that all air is expelled, and boiled for thirty minutes. The action of the formalin appears to prevent any injurious effect of heat upon the leather. However, any possible contamination of a syringe by exploratory puncture may be prevented by the insertion of a short-rubber tube with glass window between the syringe and needle, as recommended by Griffith. The fluid then does not enter the syringe at all.

An ordinary hypodermic needle is too short to insure certainty of reaching the fluid. At the same time it is usually unnecessary to employ the larger and more painful needles which are generally sold for this purpose. The one which I have always used measures one and one-half inches to the shoulder, and is of but slightly larger calibre than the ordinary hypodermic needle; it has proved quite satisfactory. The point of puncture is immaterial, so long as it is well within the flat area and above the diaphragm, as shown by percussion of the opposite side. The needle, with syringe attached, should be thrust steadily through the middle of the intercostal space; a boring motion is to be avoided as causing unnecessary pain.

By exploratory puncture we are able to establish the diagnosis of fluid; to determine the character of the exudate, whether serous, hemorrhagic, or purulent; and, finally, by its appearance and bacteriological content, to obtain valuable information as to prognosis and treatment.

The *form of empyema* can be established with certainty only by bacteriological methods, though the physical qualities of the pus are not without great suggestive value; for the latter, however, reference must be made to the section on Symptomatology. One word as to the microscopical appearance of certain bacteria: The *pneumococcus*, when colored with gentian violet, is found in chains, composed of elements which have a markedly lanceolate form, and which are nearly

always surrounded by a similarly stained capsule. The *streptococcus*, colored in the same way, appears also in chains; but the individual cocci are round instead of lanceolate, and the chains are both longer and less rigid than those of the pneumococcus. In both of these forms the only absolute test is by culture. The *bacillus tuberculosis*, unlike the preceding, is not constantly or even often discoverable, either by microscope or culture. Ehrlich, in 19 cases, found the bacillus in only 7; Netter, in 13 cases, in 5; Netter, however, obtained positive results by inoculation in all of 12 cases thus examined. A tuberculous empyema can therefore be excluded only by inoculation; and it is also to be noted that the presence of staphylococci, or of no pathogenic organisms whatever, affords strong presumptive evidence that the pus is tuberculous.

Prognosis of Pleurisy.

Primary *dry pleurisy* is almost always of short duration and favorable outcome. In from two to five days fever and pain have, as a rule, entirely disappeared. Friction may persist for some time, but eventually there is a complete return to normal conditions, with the exception of more or less adhesion between the opposite pleural layers. In rare instances, however, the primary attack is the beginning of a chronic proliferative process, which results after many years in thoracic deformity and serious invasion of the lung. Such an outcome cannot be foreseen. Secondary dry pleurisy is entirely under the dependence of the primary affection.

Serofibrinous pleurisy is also of itself a benign disease. Taking all forms and varieties, Engster saw but 3 deaths in 107 cases; Catrin only 1 death in 73. The immediate prognosis is always good, unless the pleurisy is secondary to some dangerous affection. At the present day, when the effusion is not allowed to become large, sudden death from syncope or pulmonary œdema is very exceptional. Rarely, a complicating pericarditis may necessitate caution.

As to the duration of an effusion, the prognosis must be made with more reserve. The disease has a certain tendency to pursue a cyclic course; and most small and moderate effusions of acute onset, such as constitute the majority of primary forms, disappear entirely in from four to six weeks. But in certain cases the course is more prolonged; instead of coming to a standstill at the end of eight or ten days, the effusion continues steadily to increase; or, if removed by aspiration, it persistently reforms. The prognosis of these cases is materially worse. They may recover after months of oscillation; but there is a strong liability that the eventual outcome

will be at least a permanent contraction of the chest. Sometimes an effusion, if left to itself, remains permanently unabsorbed, although the inflammatory process itself has subsided. Such a condition is not incompatible with a fair degree of health, and effusions have thus remained for ten or even twenty years. These cases, as well as the more latent forms whose onset is unnoticed, are especially apt to be tuberculous. Indeed, as we have seen, many recent authors think that seventy to eighty per cent. of all primary cases are tuberculous, but that the tendency of the majority of these is to spontaneous recovery. Whatever may be the truth, it is certain that the larger and more persistent the effusion, the greater is the probability of a permanently impaired lung and the more guarded should be the prognosis.

Attention has already been called, in considering the etiology of serofibrinous pleurisy, to another and more important relation of this disease to tuberculosis. We do not, after all, care so much as to whether all primary pleurisies are tuberculous as we do about the future health of the individual. Is he or is he not more liable to fatal forms of tuberculous disease? It seems that this question is to be answered unhesitatingly in the affirmative; and from the statistics already given, it seems that at least thirty per cent. of such individuals eventually die of phthisis. While these facts by no means justify us in filling the patient with undue alarm, they should at least lead to the exercise of the utmost prudence and caution in advising him as to his future life and occupation.

The prognosis of *empyema* can hardly be considered apart from its operative treatment. Left to itself, it is an unusually fatal affection; submitted to the benign influence of modern surgery, there are, in general, few conditions whose outcome is so satisfactory. Still, though spontaneous recovery is never to be awaited, it is not impossible. The most favorable event is evacuation by vomica, the pus gradually filtering through the lung without the production of pneumothorax. This is comparatively common in the pneumococcus form —Jaccoud says in twenty-five per cent. of all cases; Netter, in even forty per cent. It is of rather late occurrence, a case of Gerhardt's on the eighteenth day being probably the earliest recorded. An external opening through an intercostal space is far less favorable. Drainage is usually imperfect, septic absorption continues, and either the patient rapidly fails, or a fistulous opening is left behind which is liable to result eventually in amyloid degeneration of the important viscera. Still, such fistulæ have been supported for long periods of years. Other spontaneous openings than those mentioned are usually fatal, though Morgan has observed a case of recovery in which pointing occurred at the crest of the ilium.

In the rarest of instances the purulent exudate has been absorbed and a spontaneous cure effected without evacuation. Such cases have been reported by Dieulafoy, Israel, Gerhardt, and other equally reliable authorities. Most if not all of these empyemas were undoubtedly pneumococcal.

In still other exceptional cases the pus after a time entirely loses its virulence, or, perhaps, as in many tuberculous forms, it has had but little from the outset. Contained within greatly thickened walls, which resemble those of a cold abscess, it neither increases in quantity nor undergoes absorption, and may thus remain unchanged for years. While such conditions are not incompatible with a fair state of health for a time, life is sooner or later ended by the development of pulmonary phthisis or other tuberculous affection.

It is quite a different matter when an empyema is submitted to adequate and timely operation. Recovery now becomes the rule, and in certain forms of the disease is almost invariable. A few statistics will illustrate the possibilities of modern surgery in dealing with this affection. Koenig reports a series of 76 consecutive cases which have come under his care during the past twelve years; of these, 12 died—4 from pyæmia before operation, 2 from tuberculous pneumothorax, 1 from peritonitis—in fact, all from causes practically independent of the empyema. Of the 66 uncomplicated cases, 3 disappeared before recovery and were not again heard from, 3 had incurable fistulæ from pulmonary contraction, and 1 was still under treatment; the remaining 59 were all completely cured. Cabot and Eddison obtained 34 complete recoveries out of 40 cases operated upon; of the remaining, 4 died and 2 had fistulæ. Runeberg reports 58 cases treated at the Helsingfors Clinic from 1885 to 1890, all wholly cured, with the exception of 2; the average duration was fifty-two days.

The prognosis of empyema in children is even more favorable down to the age of three, under which, however, it grows progressively worse. This is shown by a number of series reported by Wightman: At the Birmingham and Midland Hospital for Sick Children, 123 patients were operated on during five years; in the 80 children over three years of age there were but 2 deaths; in the 43 under three, the deaths were 18. Again, at the Liverpool Children's Hospital, of 36 cases under three years, 18 were fatal. At Guy's Hospital, there were 19 fatal cases out of a total of 29. These figures seem to indicate that the mortality in children under three years of age is not far from fifty per cent. Above that age it is extremely small, as may be judged from the above 80 cases of Wightman, and from Holt's series of 63 operations in children, with only 2 deaths.

Probably the results in the cases collected by Koenig and Rune-

berg were unusually favorable, and would hardly represent the ordinary hazard of the average adult case. Danger may lie in the nature of the primary disease, as, for example, puerperal peritonitis, which may of itself preclude recovery; or a case may be accompanied by a suppurative pericarditis, an especially frequent and dangerous complication; or the variety of empyema may be putrid—possibly from the beginning—and thus greatly increase the chances of an unfavorable result.

It would be of great value if statistics could be given as to the mortality of the different microbic forms of empyema. Thus far very few such have been made. Netter, in 1889, reported a mortality of about 2 per cent. in cases of metapneumonic empyema, as against 15 per cent. in other forms. Prudden states that of 8 streptococcus cases, 5 resulted fatally; and of 11 pneumococcus, only 2. These statistics, though few, illustrate a point upon which there is universal agreement—*the course of pneumococcus empyema is essentially mild and benignant.* This fact has been deduced from a study of cases examined bacteriologically. It is also in remarkable accord with clinical observation, which has long noted the relatively favorable course of empyemas following pneumonia, and especially of the disease in childhood, which now appears to be pneumococcal in seventy-five per cent. of all cases. Observers are also agreed that the streptococcal form of empyema is more severe. Probably here, also, when the primary disease permits, the great majority of cases can be brought to a favorable issue. A few are unusually virulent, and from the very outset it is apparent that life is seriously threatened; Churton reports two cases, following influenza and presumably streptococcal, in which intervals of only three and four days intervened between the initial rigor and the fatal issue. Purely staphylococcal forms are likely to be tuberculous, and to pursue the same ultimately fatal course as most tuberculous processes. Other cases are so frequently associated with pyæmia that the prognosis must always be necessarily grave; still, recovery after operation is possible.

The course of tuberculous empyema is in one sense peculiarly benign. Frequently unaccompanied by fever, it may for years have no marked effect upon the general nutrition, so that the patient is able to pursue his usual occupation. Eventually, however, death occurs from some intercurrent disease, most frequently from pulmonary phthisis.

Putrid forms of empyema are the most unfavorable of all. Runeberg in ten cases had four deaths and only four complete recoveries; all of these were operated. In four cases reported by Prudden there were no recoveries.

Treatment of Pleurisy.

Initial Stage.

The first indication in a case of acute pleurisy is usually to relieve pain. For this purpose opium in some form is almost invariably necessary. The hypodermic method is preferable, since it can be repeated without danger until entire relief is assured. If the pain is less severe and there is a troublesome cough, one-half-grain doses of codeine may be given every four to six hours; or one-one-hundredth to one-fiftieth-grain doses of morphine may be prescribed hourly until the symptoms are improved.

Locally a certain amount of revulsion is desirable, both because of the relief it affords and, as some think, in order to diminish pleural congestion. Some authorities still warmly defend the local abstraction of blood by wet cups or leeches (Fraentzel, Bouillaud, Peter); and some go so far as to recommend venesection. Fraentzel, writing in 1880, advises also the use of mercurials, preferably by inunction. The great weight of opinion, especially in the United States, is strongly against these methods. It is thought that they neither prevent nor lessen the development of effusion, while it is certain that they reduce the patient's strength. French authors especially—Lancereaux, Sée, Guérin—emphasize the more or less typical course of the serofibrinous form, and even advise a purely expectant treatment. Certainly the more recent revelations as to the microbic character of most pleurisies do not favor the plan of violent antiphlogosis. There is no question, however, that a certain amount of revulsion tends to diminish pain, and to add greatly to the patient's comfort. Dry cups are at least of temporary benefit (Churton). The greatest relief is afforded by a mustard and flaxseed poultice frequently renewed. Garland recommends what he terms the "Brunton poultice," made by pouring the steaming meal into a bag made of old flannel. It does not burn, and the meal can be steamed over many times without becoming sour.

Absolute immobility of the affected side would seem to be also doubly indicated for the relief of pain and the lessening of friction. Various methods of strapping have been employed with benefit. Otto uses an ordinary cotton roller, applied so as to include as much as possible of the affected side and as little as possible of the other. He states that in all the cases in which it has been used, only once has its removal been desired. Mason prefers the elastic bandage, and others adhesive plaster; both are applied in the same manner as for a fractured rib.

Among internal remedies the salicylate of sodium seems to deserve the most confidence when the affection is apparently primary or manifestly rheumatic. Rosenbach has demonstrated the presence of salicylic acid in the serous cavities after a single dose of ten or twenty grains. The clinical evidence in favor of this remedy is strong. Aufrecht recommends it from the very onset of acute pleurisy, claiming that its effect is often rapid and that the duration of the disease is thereby much shortened. Herz has employed it for many years: he considers it a specific during the dry stage, and holds that it usually prevents effusion. Velten has had similar results. Talamon commends its employment in every stage of the serofibrinous form; it is most efficacious in the beginning, but is also valuable during the *periode d'état*, and it hastens absorption. Koester has treated 32 cases with this remedy, 27 primary and 5 secondary. Of the 27 primary cases, 17 were benefited as follows: increased diuresis, even before signs of absorption; dyspnœa lessened on the second day; rapid fall of temperature; duration of the period of absorption reduced to a "few days." While none of these reports is quite convincing, as indeed the nature of the evidence precludes, they seem at least to warrant the use of so harmless a remedy as long as no substitute is offered. The usual daily dose of salicylate of sodium is one and a half drachms. Personally I prefer the method which has given me the best results in rheumatism: ten grains every hour for twelve doses unless severe tinnitus makes it advisable to stop; then an interval of twelve hours, after which the same quantity is repeated; then after another interval of twelve hours, one drachm daily for the following week.

Rarely indications of secondary or tertiary syphilis may arouse suspicion that the pleurisy also is of syphilitic character; mercury or the iodides may then be found to have a specific action.

General treatment must be adapted to the need of the individual case. The bowels are to be kept freely open by Seidlitz powders, citrate of magnesia, Hunyadi Janos, or similar mild cathartic. Frequent cool sponging may be sufficient for the fever; or it may seem desirable to administer one of the coal-tar antipyretics, especially at night. The diet should, of course, be somewhat restricted so long as the fever continues, consisting largely of milk, with an occasional light pudding, or meat broths. Finally, and undoubtedly most important of all, the patient should be confined absolutely to bed; the temperature may be accepted as a fair measure of the continuance of inflammation, and as long as the fever lasts the recumbent posture should be enforced. The experiments of Dybkowsky, to which reference will again be made, tend to show that the inflammatory process is in-

creased by respiration; and Volland has emphasized particularly from a clinical point of view the necessity for the same absolute immobility in the inflammatory stage of pleurisy as in acute peritonitis.

Simple Effusion.

As soon as the serofibrinous character of a pleurisy becomes apparent, the indications are first to limit the amount of fluid, and later to assist in its removal.

The various methods which claim to answer the first of these indications have already been mentioned: antiphlogosis, rest in bed, immobility of the affected side, and the salicylates. If these are indicated at the outset of pleurisy, when its future character is not yet apparent, they become still more so when signs of effusion are first discovered. If pain is now much relieved or entirely gone, the poultice should be omitted and counter-irritation begun; or if the chest has been strapped, the bandage may remain until the stationary period is reached.

The removal of the fluid may be attempted by either medicinal or operative measures.

Medicinal Treatment.—The so-called Hay's method, or "dry-diet" treatment, is unquestionably the one most in favor at the present time. It is highly commended by Osler, Blakie-Smith, and Garland. This plan is based on the theory that by diminishing the watery constituents of the blood, its tendency to take up an exudate will be increased. The patient is ordered to take, once or twice a day, a brisk cathartic—preferably half an ounce of Epsom salts taken in hot water before breakfast, or a Seidlitz powder, at all events something to produce two or three watery stools. At the same time the amount of fluids ingested is limited to a pint in twenty-four hours.

In weak and debilitated individuals some caution should be observed in the exhibition of violent cathartics, the use of which is, moreover, not intended in this method. Anders has seen two cases of pleurisy in which purgation caused profound and dangerous collapse.

It is claimed for this method that it often effects the rapid absorption of small and moderate effusions even when the stationary period has persisted for several weeks. Bearing in mind the frequently cyclic course of this disease, the difficulty of furnishing conclusive evidence is apparent.

Diuretics have always been largely employed in the treatment of pleurisy. Some rely upon a milk diet, which can, however, hardly increase diuresis at the expense of an effusion. Infusion of digitalis

with the acetate of potassium (ʒ ss. and gr. xv.) is usually the diuretic preferred, and its efficiency in certain cases cannot be questioned. Garland has seen the daily quantity of urine suddenly increase from thirty to one hundred ounces and a large effusion rapidly subside under its use. Another efficient diuretic is the following:

℞ Caffeinæ citrat.,
Sodii benzoat., ... āā gr. lxxv.
M. ft. capsul. No. xxx. S. One six times daily.

Osler also mentions diuretin as very serviceable.

Diaphoretics are now seldom employed in the treatment of effusion, although several cases of rapid absorption have been observed in which an abundant diaphoresis had been accidentally produced. Fraentzel after a thorough trial of jaborandi condemns it as not only ineffectual but dangerous.

Iodide of potassium still has a few adherents, but most observers have seen no evidence that it promotes absorption.

Tonics are very often indicated, especially in the more chronic cases, and when absorption is slow. Their combination with diuretics is particularly recommended, the latter often being apparently inactive until a tonic is added; thus Fraentzel has successfully employed a five-per-cent. decoction of cinchona bark with the acetate of potassium. Anders thinks the iodide of iron is a most serviceable remedy. Here as elsewhere there is probably no more reliable ferruginous tonic than the Blaud pill.

Local *counter-irritation* would seem theoretically to be of great possible service because of the close relationship between the lymphatics of the costal pleura and those of the skin (Osler). Dybkowsky, in studying the process of pleural absorption, found that the basement membrane of the pleura is abundantly supplied with capillaries, lymphatics, and lymph spaces; the latter are separated from the pleural cavity by only a single layer of epithelial cells, and also communicate freely with the blood-vessels by means of stomata. He found that the costal pleura is especially rich in absorbents, while that of the lung, mediastinum, and diaphragm is relatively poor. Berlin blue injected into the pleural cavity was taken up largely by the costal pleura, in the lymphatics of which it could be easily traced. These observations would seem to suggest that by an irritation of the skin the costal lymphatics may be stimulated to greater activity. This accords also with general experience, and the use of iodine externally is still almost universal. It may be begun as soon as the acute symptoms have subsided, and should be continued until the effusion is wholly absorbed. Care must be taken that it is not too frequently

applied, since it may cause extreme pain when the epidermis is no longer intact. Small flying blisters, perhaps a couple of inches square, may be used instead of iodine, a fresh one being applied every two to three days in a different place. An excellent counter-irritant for these cases is the so-called Carson's paint, consisting of Ol. tiglii, ʒ ss.; Spts. ætheris, ʒ i.; and Tr. iodini co., ʒ iiss.; this may be applied twice daily until there is a considerable eruption of pustules.

When fever has disappeared, and the effusion (of small or moderate amount) has reached a standstill or has already begun to subside, the patient should be encouraged to go about. Dybkowsky concluded from his experiments that respiration is a great promoter of absorption; and it follows that a moderate amount of exercise—just enough to be a gentle stimulus to increased respiratory efforts—is directly indicated when all inflammatory action has ceased.

Thoracocentesis.—It seems hardly necessary to repeat here the familiar historical details of the development of this operation; the names of Trousseau, Dieulafoy, and Bowditch are everywhere and always associated with aspiration of the pleural cavity. Still less is it necessary to defend the merits of the procedure, as Fraentzel, writing in 1880, was compelled to do. As Rasmassen then said of his colleagues in Copenhagen, so we can now say, in the United States at least, that every physician has his aspirator. Perhaps the great fault of the present time is that thoracocentesis is too frequently performed and with too little care for those details which have made it possible to rescue the operation from obscurity, and make it one of the most beneficent of modern surgery.

The *indications* for thoracocentesis are threefold. In regard to the first two there has long been complete unanimity of opinion; the third is yet open to discussion, and somewhat different views are still expressed.

1. The *indicatio vitalis* imperatively demands the performance of aspiration whenever life is immediately threatened. Thus, suffocation may impend because of the great size of the effusion or of the rapidity with which it has formed; or the circulation may be seriously impaired, and possibly one or more attacks of syncope have already shown that the danger of delay is great.

2. *Large effusion*, even when apparently well borne, demands also immediate interference. The third rib in front is generally accepted as the limit which the fluid should not be allowed to exceed. Here compression has already begun; and the resulting displacement of the heart and great vessels involves a possibility of sudden death from syncope, or from œdema of the opposite lung. Any such possible danger must be averted.

3. *Moderate* and even *small effusions* should be removed by aspiration when spontaneous absorption is delayed beyond a certain period. Here, also, there is very general agreement, but authorities differ as to just how long to wait. Fraentzel, regarding aspiration as a procedure never to be lightly undertaken, advises puncture within the first two months. Aufrecht would aspirate only in the case of large effusions. Riegel believes in very early aspiration, even in effusions which do not reach the angle of the scapula; he regards pleuropulmonary adhesions, which prevent expansion, as the chief element of danger; "too late puncture may do harm, too early never." Lindsay thinks tapping should rarely be done in the first two weeks, but he would always tap in the third week if there were no signs of absorption. Osler would aspirate after ten days if the fluid reaches the fourth rib. B. Robinson says the effusion should never be allowed to remain stationary for more than two weeks.

These statements certainly show the general drift of opinion. While there is danger in being too precise, it seems to me that there are certain general principles involved which make it possible to establish a rather definite line of conduct. I would make the following suggestions:

When a case of acute pleurisy is under observation from the beginning, is comparatively mild, and shows a decided tendency to pursue a cyclical course, puncture need not be thought of until the stationary period—*période d'état*—has lasted from seven to ten days. Such cases are frequent and quite typical; the effusion increases during the first seven to ten days until a very moderate quantity of fluid has gathered; this is followed by a stationary period of about the same duration—during which an effort should be made, by the internal and local treatment above described, to inaugurate the process of absorption. If at the end of this period no change is perceptible, aspiration should be performed at once.

When an effusion is seen for the first time at an advanced stage of development, especially if the history is uncertain, it may be kept for a week at most under observation; unless at the end of that time it is manifestly diminishing, we must aspirate.

If there is no cyclical course, if at the end of ten to fourteen days from the onset an effusion does not come to a standstill, especially if its increase is rapid and it shows a tendency to become large, it is best to aspirate at once. It is true that this will probably be of only temporary effect, and that the fluid will rapidly return. But there is a chance that this may not happen, and even if the aspiration has to be frequently repeated, we at least prevent any dangerous accumulation and any permanent retraction of the lung.

Technique.—As to *instruments* and *apparatus* there is, in this country at least, but little room for discussion; no one ever thinks of simple puncture with a trocar. With us, since the days of Bowditch, puncture has been entirely supplanted by the use of the aspirator. Some physicians still use the original instrument of Dieulafoy: a plain cylinder and piston so arranged with stopcocks that the vacuum can first be created and then afterwards put in communication with the chest. Bowditch preferred to exhaust the barrel while it was connected with the chest, believing that he could thus better regulate the amount of suction employed.

The great majority of operators use the bottle aspirator of Potain. This familiar apparatus hardly needs description. It consists of a large bottle fitted with stopcocks which connect, by long rubber tubes, with both the aspirating needle and an air pump; a vacuum is first created in the bottle, and then by reversing the cocks this vacuum is put in communication with the chest.

The needles which come with this apparatus are of several sizes, and are partly simple hollow needles, and partly trocars. The latter are usually provided with an attachment so arranged that the air-tight perforator can be withdrawn from the cannula only just far enough to open the communication with the connecting tube. This provision has the double advantage of preventing all entrance of air into the pleura in the event of a negative intrapleural pressure, and also of making it very easy, by simply thrusting in the perforator, to remove any possible obstruction of the cannula. In favor of the hollow needle is its smaller size, and its less painful and easier penetration. The question of size is quite important; that to be preferred is the one corresponding to the No. 2 needle of the Dieulafoy apparatus. Much of the favor which aspiration has won in modern times is unquestionably due to the change from the large trocar of the earlier operators to the almost capillary needle of to-day. Sudden death from œdema and syncope was not infrequent when large quantities of fluid were rapidly withdrawn. On the other hand, the entrance of even minimum quantities of air into the pleural cavity is certainly undesirable; though probably innocuous in the very great majority of cases, such air may contain pathogenic microbes which give rise to suppuration. It is evident that when a simple hollow needle is introduced into the pleural cavity, the air which it and the connecting tube contain will be inevitably sucked into the pleura, if the pressure chances to be negative. Although a positive intrapleural pressure invariably prevailed in the long series of cases tested by Leyden, at least at the beginning of aspiration, it is to be considered that it was not then customary to puncture so early and in such small

effusions as now. Furthermore, the needle often becomes clogged; and the only alternatives are then to remove and puncture again, as advised by Bowditch, or to clear it with a wire and thus provide an extremely favorable opportunity for the entrance of air. Personally I have nearly always used the hollow needle, and have never seen any disastrous result. Koenig also gives expression to considerable doubt whether the entrance of air into the pleura is at all likely to produce infection. Still, the smallest trocar is probably the safest instrument to use. If after puncture the air is first exhausted from flask and tube, the perforator then withdrawn from the cannula beyond the stopcock, and the latter closed, all possibility of the entrance of even a single bubble of air is excluded.

It need hardly be said that in aspiration no less than in more formidable operations, every aseptic precaution should be rigorously observed. Hands, instruments, and the patient's skin should be as carefully sterilized as for a thoracotomy. Particular stress is to be laid upon a thorough disinfection of the needle by boiling; probably a dirty needle has been much oftener responsible than the entrance of air for the conversion of a serous exudate into pus.

The *site of puncture* is not a matter of very great moment. Some choose the fifth interspace near the mammary line, some the fifth or sixth space in the axilla, and others the eighth or ninth in a line with the angle of the scapula. Fraentzel objects to the latter, on the ground that the muscles are there thicker, the danger of piercing the diaphragm is greater, and the needle is more apt to enter a mass of fibrinous deposit. As a matter of fact, in a large proportion of cases the effusion does not extend in front of the axillary line, and there is no choice. I myself prefer the posterior site, and have never felt the force of Fraentzel's objections.

The position of the patient during aspiration may be either upright, or semi-recumbent and partially rotated towards the sound side. Bowditch had him sit sidewise in a chair, with arm resting over the back. General anæsthesia is never necessary; but it is well to lessen the pain when it can be done by so harmless a procedure as the injection of ten drops or so of a one-per-cent. solution of cocaine; I have thus punctured children even without so much as a word of complaint. The administration of an ounce of whiskey is often a good prelude to the operation.

After definitely fixing the selected interspace with the point of the left index finger, the needle is entered rather carefully until it has engaged between the ribs, when it is thrust steadily and vigorously forward into the pleural cavity. A slow boring motion of the needle is to be avoided; it not only increases pain, but makes it possible

that the needle may, as suggested by Fraentzel, push away instead of pierce the costal pleura. An instance of what seemed to be this accident has come under my own observation. The advice is usually given to hug the upper border of the lower rib in order to avoid wounding the intercostal artery. This danger is to be regarded as somewhat chimerical, and it is far better to aim at the middle of the space and thus save the patient a painful mutilation of a rib. The presence of fluid should always be demonstrated by exploratory puncture before aspiration is attempted.

The *amount of fluid to be withdrawn* is perhaps the most important consideration connected with thoracocentesis. We have already seen, under Complications, that the removal of a large quantity at a single sitting may result in a dangerous œdema of the affected lung; sudden death from œdema or syncope not infrequently followed the operation as it used to be performed, and added greatly to its discredit. The favor in which thoracocentesis is now held dates from the introduction by Bowditch of aspiration through a very small needle; and it is unquestionably in the *slow withdrawal of only a moderate quantity of fluid* that the safety of aspiration lies as compared with the old method of puncture with a trocar. Dieulafoy found, for example, that of sixteen cases of "albuminous" expectoration, aspiration had been used in only four; and furthermore, he was unable to find a single reported case of death from aspiration when not more than 1,200 c.c. of fluid had been withdrawn. These facts ought not to be forgotten or disregarded. A good and safe rule is never to withdraw more than three pints of fluid at once, and seldom more than two. If the effusion is very large, the aspiration should be repeated every two or three days until the greater portion is removed. To empty the pleural cavity completely is unnecessary; the aspiration of a small quantity is often sufficient to relieve the pressure upon the lymph spaces or stomata, and to effect a rapid absorption of what is left. There is, however, no objection to removing all if the above limit be not exceeded.

But it may happen that even before two pints have been withdrawn, certain disagreeable symptoms appear which make it necessary to desist. These are pain in the chest, a feeling of great constriction, suffocation, or faintness, and uncontrollable paroxysms of cough. Fraentzel states that he is no longer troubled by the latter since he aspirates slowly—meaning by "slowly" the consumption of at least thirty minutes in the removal of three pints. However this may be, if any of these symptoms appear, an immediate pause should be made in aspiration; after a few moments it may be cautiously resumed, but a second attack demands an immediate withdrawal of the needle.

The wound is perhaps best treated by a regular surgical dressing. I usually apply a square of adhesive plaster and have never seen any unfortunate result.

Among the minor accidents of aspiration are puncture of the lung, diaphragm, liver, or spleen. Though I must plead guilty of all of these errors in connection with exploratory puncture, I have never seen any unpleasant consequences, although they are of course to be avoided. Fraentzel relates a unique case of fatal pulmonary hemorrhage after aspiration; it was caused by the rupture of a miliary aneurysm in a tuberculous cavity of the affected lung.

The first twenty-four hours after paracentesis should be spent in bed. The patient, if all is well, may then go about, and the subsequent treatment should be similar in all respects to that of a spontaneous absorption. In either case the local use of counter-irritants may be continued together with the internal administration of mild diuretics and tonics. As absorption progresses, an attempt should be made to aid as far as possible in effecting a complete reexpansion of the lung. Osler speaks highly of the use, once or twice daily, of the Wolff bottles—two large bottles so arranged with tubes that by blowing into one the water with which it is partly filled is driven into the other; and so on, back and forth, as long as may seem desirable; the expiratory expansion thus effected can hardly fail to be of service. A change of climate is often of the greatest benefit, particularly removal to a mountainous region like the Adirondacks or Colorado; not only because of its effect upon general nutrition, but also because residence in an elevated region furnishes an excellent form of mild and continuous pulmonary exercise. Where this is impossible a certain amount of daily out-of-door exercise should be enjoined—walking, and later bicycling, or even running. During the winter months moderate gymnastic exercise, as with light wall weights or Indian clubs, will be a useful adjuvant.

But even when all local signs have disappeared these patients should still be kept under observation. It seems to me especially desirable that in most cases of primary pleurisy the patient himself, or at least his intimate friends, should be made acquainted with his special liability to pulmonary tuberculosis. This can be done in such a way that without being made unduly apprehensive the patient will avoid exposure, and particularly give timely heed to such initial symptoms as a loss of flesh or a constant cough. He should understand that the slightest symptoms referable to the chest should lead him at once to seek medical advice. Every one knows that it is only in its initial stage that pulmonary phthisis is curable; and a physician who should fail to advise a former sufferer from pleurisy to seek

a favorable climate at the very first suspicion of tuberculosis would be guilty of a fault which, in the light of our present knowledge, must be considered wholly unpardonable.

The treatment of the *chronic and latent forms of pleurisy* is less promising. Repeated aspiration must be combined with the application of local irritants and the exhibition of tonics; any prolonged course of purgation or diuretics would of course be a mistake. Here, also, most is to be hoped for from general hygienic measures, among which an out-of-door life in a suitable climate is the main factor.

Empyema.

There is practically but one treatment for purulent pleurisy—the immediate evacuation of the pus by operative procedure. Four principal methods are in use at the present time:

Aspiration.—This operation is entirely inadequate for the great majority of empyemas. It does not provide for free drainage, which is usually essential to a successful result. On the other hand, it is undeniable that a certain number of empyemas may be entirely cured by one or two aspirations. Holt collected 121 cases in which this method was tried; he found that 23 were cured, 6 died, and 92 came to further operation. Holt cites this series as an argument against aspiration; it seems to me rather to suggest a further search into the reason for such a marked difference in cases, and its practical application. If even twenty per cent. of all cases can be cured by so simple a procedure as this, it would hardly seem that it is an operation to be lightly condemned. The great trouble has always been not so much with aspiration itself as with the indiscriminate way in which it has been employed; and the following recommendation of its use under certain conditions is to be understood as always with the distinct proviso, first, that the case is mild, and that there is no apparent danger in delay; and second, that the operation, if unsuccessful in producing a complete reduction of temperature, shall be repeated only once at most, and then give immediate place to more radical measures.

This method is indicated in those empyemas of childhood which are known or appear to be of pneumococcal origin. It has always been in children that aspiration has been relatively successful, and that this is because such empyemas are usually produced by the short-lived and comparatively non-virulent pneumococcus has already been sufficiently emphasized. It is true that most American pediatric physicians prefer immediate radical operation in all cases (Jacobi, Holt, Huber, Beck). Rotch, however, believes in preliminary aspiration; and

Henoch also recommended this plan long before it had the scientific basis which it has to-day. Its advocates on the Continent are now numerous, among others Netter, Gerhardt, Jaccoud, Debove, Ferdinand, Courtois-Suffit, and von Ziemssen. In cases not manifestly metapneumonic, the diagnosis should be confirmed by a bacteriological examination of the pus obtained on exploratory puncture. In any event, unless improvement is pronounced, not more than a week should be allowed to elapse after the first aspiration before resorting to the radical cure.

In the pneumococcal empyemas of adults most French authorities also advise the same procedure. Netter reports ten successful results. If the diagnosis be fully established, there seems to be no good reason why the chance of success should not be nearly as good as in children, and why the patient should not have the benefit of the doubt. To the patient, at least, incision is a far more formidable operation than simple puncture; it means, as a rule, anæsthesia, an incapacity of a couple of months' duration, and considerable expense. Moreover, after aspiration there is a better chance of an immediate and complete expansion of the lung. All these considerations are not to be despised; they are not offset by a possible delay of a week, when the patient has but little fever and is in fairly good condition.

Aspiration is indicated in all forms of empyema when the patient is in danger, but when his condition is not such as to warrant an immediate radical operation. Thus extreme weakness, or an œdema of the lung, or a threatening syncope, or other equally dangerous complication, may make a partial removal of the fluid immediately necessary. Usually, however, the radical operation should be deferred only for a few hours, and the cases in which even this is necessary are not frequent.

In certain cases of tuberculous empyema it is an open question whether aspiration is not a more conservative method of treatment than thoracotomy. Assuredly not in all cases—not when there is a high range of temperature, nor when an acute empyema is simply associated with a mild degree of pulmonary phthisis; such patients should be treated like any other sufferer from empyema. But if the empyema is absolutely latent; if it has lasted already for an indefinite period; if the patient has an incurable form of pulmonary phthisis, and yet is still maintaining a fair degree of general health, it is a serious question whether the radical operation will not cause a change for the worse.

In any case, an annoying and often permanent fistula will be established, and both the drain upon the system and the danger of amyloid degeneration will be materially increased. It is further to

be considered that the more or less quiescent tuberculosis of the compressed lung may be aroused to fresh activity by such partial expansion as follows either thoracotomy or aspiration (Czernicki, Bäumler). On the other hand, such a tuberculous empyema, if left to itself, is not inconsistent with fairly good health for an indefinite period; instances are on record in which life has been prolonged for ten or even twenty years (Fraentzel). Or, if aspirated, the effusion may not recur for a long time, and even resorption of these often chylous or fatty exudations has been observed. It is seen, therefore, that the chances of radical operation are not tempting. Moutard-Martin operated in seven cases; all died. Kroenlein lost eight out of fifteen; Runeberg three out of four. It is not surprising that many eminent authorities—Netter, Fraentzel, Godlee—practise non-interference in many of these cases, unless a dangerous growth of the effusion makes it imperative to aspirate.

Simple Incision.—For reasons which will presently appear, incision is not the operation of choice in the empyemas of adult life. It has, however, one great advantage over resection—it can be done without general anæsthesia, and on this account it may occasionally be advisable simply to incise in cases in which an anæsthetic would be dangerous. Furthermore, incision is generally preferred to resection in children (Morrison, Holt, Huber, Jacobi). That it offers all the necessary conditions of success is shown by Morrison's seris of thirty-four cases in which there were only two deaths and the average duration of the treatment was but thirty-two days. Local anæsthesia may be effected by the injection of a one-per-cent. solution of cocaine, or, as recommended by Powell, by the application of a small cake of ice which has been dipped in salt. Although such local anæsthesia is all that is absolutely required, there is in most cases no contraindication to a general anæsthetic, chloroform being commonly preferred.

In regard to the best site for thoracotomy there is no general agreement. Probably a majority of operators prefer the fourth, fifth, or sixth interspace in the axillary line; Koenig says the fourth is the best. Others always operate just below the angle of the scapula. The objection usually made to this location is that the diaphragm is apt to rise and block up the opening of the drainage tube. Practically the results are equally good in both; and there is occasionally no opportunity for choice because the effusion is small.

The operation itself is simple, but it should be none the less strictly aseptic in all its details. The best position is the lateral semi-recumbent, with arm raised above the head. The skin and soft tissues are quickly incised down to the intercostal muscles. The

latter may then be slowly divided between two retractors, as advised by Fraentzel; or the knife may be thrust rapidly into the pleural cavity, and the opening then sufficiently enlarged with an ordinary sinus dilator. Steele uses a pointed grooved director which is first inserted to guide the knife.

The incision should be as close as possible to the lower rib in order to avoid the intercostal artery. As soon as the incision is complete, one or two fingers should be inserted in order that the escape of pus may be slow; a too rapid evacuation of the pleural cavity is attended with the same danger as a too abundant aspiration. A large drain, guarded by two safety pins, is then introduced, and a surgical dressing is applied in the way that will be described in the following section.

Thoracotomy with Resection.—Operators are certainly few who do not prefer the resection of an inch or so of one rib to simple incision in most empyemas of adult life. While general anæsthesia is always necessary in resection, its advantages over incision are very considerable. The most unanswerable argument in its favor is that it has seemed to give better results. Simonett found that 107 cases of incision were followed by 60 complete cures, or 56 per cent., and 12 fistulæ; 79 cases of resection gave 55 complete cures, or 70 per cent., and only 6 fistulæ. The unusually brilliant results also of Koenig and Runeberg (see Prognosis) were obtained by resection. Again, this operation gives room for a larger tube and freer drainage; the fistula is not so likely to become narrow and oblique. Laache thinks its chief excellence lies in the fact that with better drainage irrigation becomes superfluous. Beck, writing upon the results of resection in 138 cases, claims that it enables the operator to insert the finger and, by sweeping it about, to open up thoroughly all pockets of pus, and tear off any adherent clumps which would interfere with complete drainage. At all events, this operation is now preferred, for one reason or another, by probably the great majority of all surgeons.

Resection is indicated in all cases and forms of empyema not already included under aspiration or incision. Even when spontaneous evacuation has already occurred, whether by vomica or by empyema necessitatis, the indication for the operation is no less imperative.

Of the anæsthetics chloroform is generally chosen, because it is less irritating to the bronchi, also because it is apt to cause less struggling and less consequent danger of rupture into the lung and immediate suffocation. Morrison says that the patient should not be turned over after he is anæsthetized. The danger of either chloro-

form or ether is to be regarded as somewhat greater than in other operations.

As to the site of incision, the position of the patient, and the necessity for thorough asepsis, nothing need be added to what has already been said in the preceding section. Resection is a safe and easy operation which no well-trained physician need hesitate to perform. A single cut, three inches in length, will lay bare the rib. While the wound is held open by the aid of retractors, the periosteum is crowded to each side by an elevator until the outer surface of the rib is denuded to an extent of about two inches. The same is done along the edges and underneath until the rib is entirely separated from its attachments to the soft parts. It is then grasped by strong forceps, and by the use of any of the specially designed rib cutters, or of an ordinary bone forceps, a piece about one and a half inches long is excised; this does not sever the intercostal artery which has been separated from the bone with the periosteum. If care has been taken the pleura is still intact, and is now opened by a small incision. The forefinger is then inserted and swept about the walls in every direction to clear away any pockets or fibrinous clumps; it is then held in the wound in such a way that the exit of the pus is slow. By the time this is finished the patient will have partially recovered from the anæsthetic. He can now be turned upon the affected side, and lifted, first by the legs and then by the shoulders, in such a way that the chest will at last become thoroughly emptied.

At this stage it has always been customary, until within a very short time, to irrigate the pleural cavity; and it has also been thought necessary to repeat these irrigations later at frequent intervals until recovery was complete. The last few years have seen the almost complete abandonment, first of the subsequent irrigations, and finally also of the one at the time of operation. The objections to irrigation are, first, that it is unnecessary and indeed actually retards recovery, and second, that it is dangerous. This latter objection has always been admitted; the occasional forms of sudden death, "pleural epilepsy," convulsive seizures, and the like, incident to washing and other manipulations, have already been fully described in the section on Complications. But it has been supposed that the advantages of lavage far outweighed the possibility of these accidents, and its use has been continued. It now appears, however, that irrigation prolongs the suppurative process. Runeberg's observations in this connection are extremely suggestive if not convincing: From 1876 to 1880 all empyemas treated at the clinic of Helsingfors were irrigated daily; the average duration was 101 days, and there were 30 per cent. of complete cures. From 1883 to 1885 a single lavage

only was made at the time of operation; the average duration fell to 84 days, and the cures increased to 70 per cent. From 1885 to 1890 irrigation has been discarded entirely except in putrid cases; in 48 uncomplicated cases the duration was 52 days, and 46, or 96 per cent., were cured. While due allowance should be made, as Runeberg says, for the influence of other factors, that of irrigation seems to be dominant.

The shortest case of empyema which ever occurred in my own practice was metapneumonic in a man of thirty-four; resection evacuated about two pints of thick pus; there was no lavage at the time of operation or afterward; complete and permanent cure occurred in ten days under only two dressings.

Among those who besides Runeberg have also done away with irgation are Laache, Beck, Koenig, Bucquoy, and Morrison. In putrid empyema irrigation is still practised by most operators, though Hertz finds that simple resection and drainage are here also sufficient to effect a cure. The pleural cavity should be thoroughly irrigated once, or, in severe cases, twice a day. It is best for this purpose to use a weak solution of either boric or salicylic acid, and finally to disinfect by a 1:2000 sublimate solution (Koenig) which is then immediately drained off. Occasionally a putrid empyema is best treated by making a second incision at the posterior base close to the spine.

After incision and thorough emptying of the chest a drainage tube, well powdered with iodoform, is introduced. This is prevented from slipping into the chest by two or three large safety pins, which transfix its outer end in such a way as not to obstruct the flow, and from which if necessary strips of gauze may be carried around the chest and tied. The tube should be as large as the finger, and two and a half to three inches in length.

I am in the habit of closing the external wound on each side of the drain by two or three deep stitches; first intention is usually obtained, and a large granulating surface is thus avoided.

A layer or two of iodoform gauze should be laid between the safety pins and skin to prevent an ulcerative indentation. The dressing should be *lege artis*, and extremely large: iodoform gauze over and about the tube, then a dozen layers of sterilized gauze, covered by an immense pad of sterilized cotton which envelops the whole side from clavicle to cresta ilii. The axilla should be especially padded; Koenig includes even the arm.

The after-treatment is, according to Koenig, a no less essential feature than the operation itself. Two things are especially important,

namely, the change of dressings and effectual drainage. The guide to the former is the saturation of the dressing with pus, as shown by its appearance externally, and the temperature. In the event of either fever or moisture the dressing must be immediately changed. In some cases the first dressing may remain a week; oftener it must be removed in a day or two (aseptic precautions), while the second need not be disturbed for several days. Rarely it is necessary to dress daily. Perfect drainage must be assured by an appropriate position of the patient. The plan pursued by Koenig has been attended with such excellent results that it may here be described. The patient is made to lie as much as possible on the affected side. Four times daily during the first week, and later two or three times a day, he is lifted by an attendant as follows: first, in the lateral posture, he is raised by the trunk and lower extremities, so as to rest for a moment upon the shoulder, this drains from below; he is then lifted by the shoulders to insure drainage from above; and finally, the first movement is repeated. If the patient is very heavy he can so hang the shoulders over the edge of the bed that the same drainage from below is accomplished without assistance.

A few days after the operation the patient may go about if there is little or no fever and not very much discharge. It is best, however, for him to lie for a while each day on the affected side, and to go through the above-described movements.

The final removal of the tube must be determined by the amount of discharge, and by a careful probing of the fistula with a soft catheter. Not infrequently it is found in the dressing and cannot be put back; in this event, if the quantity of pus is already small, the question may be regarded as having settled itself.

Siphon Drainage.—This so-called "method of Bülau" has found but little favor outside of Germany, and even there it is used by only a few operators, among whom are Immermann, Curschmann, Leyden, and Sahli. The chest is first punctured with a large trocar, some 6 to 13 mm. in diameter. After most of the pus is thus withdrawn, a soft-rubber catheter is inserted through the cannula into the chest, and over it the cannula is removed. To this catheter is attached a long rubber tube, the other end of which passes to the bottom of a bottle partly filled with an antiseptic fluid, or into a larger jar at the side of the bed. The pus is thus continuously siphoned from the chest into the bottle, while if at any time the siphon is broken there is no possibility of a backflow of air into the chest. Various objections are made to this method—that drainage is imperfect and unsatisfactory, that the tube becomes frequently obstructed, that it eventually becomes loose, that the bottle has to be carried about, and so on. None

of these can be considered valid if the ultimate results are favorable; and these results certainly seem to have been good. Sahli reports twelve cases thus treated, the duration of which varied from twelve to seventy-two days; Curschmann had sixty-three good results in seventy-five cases. Without having seen any actual trial of this method, it seems to me that in selected cases it might be of considerable value. It is usually thought to be inapplicable to children, but Patton appears to have treated large numbers in this way with satisfactory results. A possible field of usefulness is especially the chronic tuberculous form of empyema, and perhaps also the pneumococcal empyemas of adults.

Such are the various operations for empyema and their special indications. If these fail, if the cavity does not close, and after months or years the fistula still continues to discharge, there still remains a possibility of cure by the operation known as *thoracoplasty* —also commonly called the *operation of Estlander.* By the removal of a section of several ribs, the thoracic wall is enabled to sink in and helps to fill the suppurating cavity. When the fistula persists simply because the lung cannot expand, the usefulness of this operation is often very great. Koenig, however, believes that this indication is rare, and that most fistulæ are ept open by a caries, or by a small pocket of pus concealed somewhere beneath a rib, or by some suppurative process of the lung itself; in such cases an extensive resection would be of little service. For the details of the operation, and for other methods of dealing with such fistulæ, I must refer to works on special surgery.

A word may here be said in regard to the phenomenon of re-expansion of the lung while there is still a pleural fistula. Is it the result of an inspiratory or expiratory force; and what prevents subsequent collapse? In the first place it is to be remarked that at the time of the operation of an empyema the lung will often immediately expand so as to be palpable in the wound; I myself have seen this, and it is a matter of very general experience. Here it is manifest that inspiration can have absolutely no effect upon the lung, since the external opening is large and free, and no vacuum can possibly be created in the pleural cavity. The only force capable of such an effect is an expiratory one, such, for example, as occurs with cough, when the glottis is closed and the thorax contracts violently upon the contained air. Once expanded, the lung can avoid subsequent collapse in only three possible ways: either it is held from without by some force of cohesion, or from within by inability of the air to escape, or because it has lost some of its retractile power. As to cohesion, the

experiments of Northrup certainly demonstrate that under normal conditions, at least, it is not sufficient to overcome the retractile power of the lung; whether this is also true under diseased conditions is uncertain; it seems quite possible that this cohesion may be materially increased when the pleural surfaces are inflamed. On the other hand, neither of the other suppositions in regard to the lung itself is inconceivable. That normally the air contained in the terminal alveoli cannot wholly and immediately escape is very probable; for instance, in Northrup's experiments an animal with double artificial pneumothorax did not at once suffer the great distress which afterward developed. O'Dwyer suggests the possibility of a force of attraction between the oxygen of the air and the hæmoglobin of the pulmonary capillaries which may exercise a certain restraining effect upon the air. Again, a lung which has been long compressed may have temporarily lost much of its retractility; and these two factors combined, to which possibly a certain degree of cohesion may be added, may be sufficient to maintain the lung, for a while at least, in the inspiratory position. Later we may admit with Aufrecht that inspiratory efforts have much to do with the reexpansion of the lung, when the external opening is covered with a bandage, or is so small that a partial intrapleural vacuum with deep inspiration is not impossible; the gradual development of adhesions (Fraentzel, Aufrecht) may then enable the lung to maintain the advantage thus gained.

The treatment of certain special forms of empyema has not yet been mentioned. In *double empyema* it is usually deemed best to operate upon the two sides at an interval of five to ten days. *Encapsulated* empyema should be treated like any other; here of course the site of incision is not a matter of choice. *Existing perforation*, whether the result of vomica or external fistula, should alter in no wise the site of operation. Any attempt to dilate the fistula and insert a drain will probably be of little or no benefit. Resection is here especially desirable, and it should be done, as usual, in the axillary or posterior region.

The subsequent general and hygienic treatment of an empyema, after the fistula has closed, does not differ from that of serofibrinous effusion when absorption is nearly complete. Here especially every effort should be made to bring about full expansion of the lung. The Wolff's bottles are adjuvants; so are also light gymnastics. In most cases nothing could better meet the indications than the tonic effect, both upon the general constitution and the lung, of mountain climbing or other out-of-door exercise in an elevated region like Colorado.

PNEUMOTHORAX.

Definition.—An accumulation of air in the pleural cavity. The combination of both air and serum constitutes a pneumohydrothorax; of air and pus, a pneumopyothorax; or if air and blood are found together, a pneumohæmothorax is said to exist.

Etiology.

Up to the time of Itard, in the early part of the present century, gas in the pleural cavity had only been remarked as an occasional post-mortem occurrence. Itard first called especial attention to this condition during life, and gave it the name which it now bears. He supposed that it was due to a decomposition of pus which had resulted from the breaking down of the lung. Laennec then showed that the lung was simply compressed, not destroyed. He recognized, too, that the condition was often caused by pleural perforation; but he also supposed that many cases were produced by the decomposition of pus, and even that in some instances gas was secreted by the pleural wall. Later investigation demonstrated more and more conclusively that the great majority of cases were due to perforation, and a critical examination of the instances of so-called "essential" pneumothorax showed that most of these cases could readily be accounted for on the same basis. At the present time, it is the general belief that pneumothorax always results from perforation, although a few—Weil, Biermer, and Senator, among others—still hold that gas may exceptionally develop from decomposition. A recent observation of Levy is of remarkable interest as apparently confirming this, the original view of Laennec. In an individual with pneumothorax following pleuritic effusion, culture of the aspirated fluid showed an anaërobic microbe, in the form of short, thick rods with rounded ends, which possessed the function of rapidly developing gas; this occurred both in the culture medium and in the tissues of guinea-pigs, in which inoculation produced a gaseous phlegmon at the site of injection. A post-mortem examination and careful search failed to show any perforation in Levy's case, and it is regarded by Dippe as absolutely demonstrating the spontaneous development of pneumothorax from decomposition. But even if this should be confirmed, it would not change the almost universal rule that pneumothorax is caused by the entrance of air into the pleural cavity from without by perforation. It is always, therefore, a secondary disease.

The primary condition which is responsible for pleural perforation in a very great majority of cases is *pulmonary tuberculosis*. Walshe,

Weil, Powell, and Fraentzel all agree in ascribing at least ninety per cent. of all cases to this cause; and the individual experience of every practitioner cannot fail to confirm this estimate. On the other hand, the proportion of phthisical subjects thus attacked is not large. It is usually stated to be from 3 to 5 per cent.; thus Eichhorst found only 5 per cent. among 390 cases of phthisis; Gutmann in the autopsical records of 2,200 cases of the latter, found pneumothorax noted in only 4.2 per cent. Weil's results were somewhat different, pneumothorax being present in over 10 per cent. of 355 cases thus examined.

Pulmonary phthisis gives rise to pneumothorax through the softening and rupture of a superficial tuberculous nodule. A large pulmonary cavity may also occasionally break into the pleura; but such cavities rarely reach the surface of the lung without being preceded by an adhesive pleurisy which exercises here an extremely beneficent and conservative function. Pneumothorax is therefore most likely to be associated with the earlier and more acute forms of phthisis, from the rapid development and softening of fresh tuberculous nodules; these nodules may sometimes originate in the pleura; probably as a rule they develop in the lung itself. At the same time pneumothorax is not confined to any one stage or form, and is certainly common enough as a terminal condition in all varieties of chronic phthisis. As a rare circumstance may be mentioned the occurrence of pneumothorax in phthisis from the rupture of an emphysematous vesicle (Gaillard, Zahn).

Of the ten per cent. or so of cases which are not referable to phthisis, more are the result of *empyema* than of any other one cause. We have already seen that it is not an uncommon event for empyema pus to find a way of escape through the lung, especially in the pneumococcal form. Usually pneumothorax does not accompany vomica; the pus filters through the pulmonary tissue in such a way that the air gets no opportunity to enter the pleural cavity. But there are exceptions to this rule; and a larger spot of necrosis, or a direct tear into a bronchus with sudden evacuation of large quantities of pus, makes a pneumothorax unavoidable.

Other causes of pneumothorax are individually rare, and include, besides trauma, most of the destructive processes which involve the neighboring organs. Traumatic pneumothorax may arise from all sorts of penetrating wounds, among which operation for empyema is the most frequent; from fracture of a rib, without necessarily any external wound, both pleura and lung being lacerated by the broken ends; also from severe contusion or even concussion of the chest, the lung being simply ruptured by violent compression. Here also should be included those rare forms of pneumothorax

which have resulted from traumatic perforation of the œsophagus, as by a fishbone, or from bougies used for stricture—for example, the case of Buss in which death occurred in four days from putrid pneumothorax, and the sound was found to have passed directly into the pleural cavity.

Destructive processes which may produce pneumothorax are the following:

(*a*) Pulmonary: *Gangrene* of the lung, rarely the classical affection, oftener the disseminated form such as results from small pyæmic emboli in connection with ulcerative endocarditis or pylephlebitis and after operations. *Bronchiectasis*, when putridity has developed with consequent necrosis of the bronchial wall; here the resulting pneumopyothorax is also putrid. *Bronchopneumonia*, according to Rilliet and Barthez not an uncommon cause in children, and producing pneumothorax by the rupture of minute superficial abscesses which these authors term vacuoles. Finally, *pulmonary abscesses* from croupous pneumonia or infarction—a very exceptional cause; *cancer* of the lung, and in rare instances an *hydatid cyst.*

(*b*) Mediastinal: *Softening of the bronchial glands* and resulting communication with both œsophagus and pleura; *œsophageal ulceration* from either cancer or stricture.

(*c*) Abdominal: Especially *abscesses* such as may originate in an *ulcer of the stomach* or *duodenum*, and by breaking into the pleura connect the latter with the gastrointestinal canal; *abscesses and suppurating cysts of the liver*, also *nephritic* and *perinephritic abscesses*, which make their way through the adherent pleuræ into the lung, with subsequent rupture of the phrenopulmonary adhesions (Netter).

Pneumothorax in children has already been alluded to as occasionally resulting from pneumonia. Sevestre has even observed two cases at the age of sixteen months, one in connection with bronchopneumonia, and the other with hereditary syphilis. Cnopf has called particular attention to pneumothorax in childhood, and finds that in addition to occasional forms corresponding to those in adults, another may be met with in connection with diphtheria and tracheotomy. Cnopf has seen four of these cases, all after tracheotomy, and considers them due to rupture of an anæmic lung.

Still another and not the least interesting form of pneumothorax remains to be considered—that commonly known as "accidental," formerly also termed "essential" pneumothorax, because it was supposed to be idiopathic. Its characteristic feature is its occurrence in individuals who have always been in seemingly perfect health, and who remain so after recovery. Gaillard has analyzed thirty-seven cases of this sort, among them twenty-two in which the pneumothorax

was not followed by effusion. The form usually develops suddenly without adequate exciting cause; and it is the opinion of Gaillard, in which he is supported by most authorities, that a considerable proportion of these cases is due to emphysema, but not to the typical form of chronic inveterate emphysema associated with asthma; pneumothorax may indeed follow this form, but it does so very rarely, as shown by the fact that Gaillard could collect but twelve instances. In early life also, in spite of the frequency of emphysema with bronchopneumonia and whooping-cough, resulting pneumothorax is very unusual. It is rather to the vicarious and localized emphysemas of young adults that Gaillard refers, and he explains this apparent paradox as follows: For the production of pneumothorax by the rupture of an emphysematous vesicle there must be a corresponding rupture of its pleural investment; in the young and very old the subpleural connective tissue is more relaxed and yielding than in early adult life, in which the pleura is firmly adherent to the subjacent lung, so that the rupture of one involves that of the other. Only three of Gaillards' cases came to autopsy; in all a ruptured vesicle was found, and in none was there the least evidence of tuberculosis. Still, it is the opinion of some authorities that all such cases are really tuberculous. The form is infrequent as may be inferred from the limited number of cases (thirty-seven) collected by Gaillard.

The acute pleurisy with serofibrinous or purulent effusion, which is an almost invariable result of pneumothorax, is rarely if ever due to the simple presence of air. Upon this point there is entire agreement between the results of experiment (Wintrich, Weil, more recently those of Szupak on the injection of pure air into the pleural cavity of dogs) and clinical observation. In the accidental forms—such as presumably result from simple rupture of the lung—there is often no pleurisy whatever, and the course of the disease is extremely benign. Here recent studies in the etiology of pleurisy (see the section on Etiology of Serofibrinous and Purulent Pleurisy) are of great suggestive value and leave but little doubt that the essential element here as elsewhere is microbic infection. The bacillus tuberculosis alone appears to produce only the serofibrinous form. It can rarely be demonstrated by the microscope or culture, but inoculation seems to have given invariably positive results in the few cases in which it has been tried. Netter, for example, in twelve cases of inoculation, did not fail once to produce tuberculosis.

On the other hand we may safely affirm that a pneumopyothorax can occur only when, in addition to air and the bacillus tuberculosis, pyogenic organisms have entered the pleural cavity. In three cases examined Netter found the staphylococcus pyogenes together with

certain saprogenic germs; undoubtedly the latter predominate in the putrid form. The streptococcus also is probably concerned in the production of many cases—the pneumococcus rarely, since pneumothorax is seldom associated with pneumonia. That many cases of accidental and an occasional tuberculous pneumothorax should not be followed by pleural inflammation is not difficult to understand. It is well known that the air of the terminal alveoli is normally in a condition of great purity; and it is not surprising that with the simple rupture of a superficial vesicle the pleural cavity should escape infection.

Pneumothorax corresponding to its usual phthisical origin is a disease largely of young adults. It occurs somewhat oftener in males than in females, and twice as often in the left as in the right pleural cavity. The immediate exciting cause of pneumothorax may be any marked expiratory effort such as a hearty laugh or a sneeze, lifting, straining at stool, and especially cough. Oftenest no cause is to be discovered; Weil found none in about ninety per cent. of his cases.

Pathological Anatomy.

The affected side is seen to be dilated, with more or less obliteration of the intercostal spaces. On puncture the air, if under positive pressure, will escape with a perceptible hissing sound, and possibly with sufficient force to extinguish a lighted candle. The pleural cavity when opened may appear as a large empty space occupying more than half of the thorax; the heart, mediastinum, and diaphragm are much displaced, and the lung is compressed to one-fifth, or even less, of its usual size. Usually, however, the cavity contains a varying quantity of fluid; its walls are covered with an irregular layer of fibrin, and if this be removed the pleura beneath shows all the usual evidences of inflammation (see Dry Pleurisy).

The lung, on closer examination, is found to be compressed upwards, inwards, and backwards against the spine into a small fleshy mass about the size of the two fists. Its color, when not concealed by fibrinous deposits, is bluish or reddish brown. The perforation may appear as a rent half an inch or more in length, as for instance in connection with gangrene; oftener it is not larger than a pin's head and is very difficult to detect on simple inspection; if, however, the lung be inflated under water the escape of bubbles will usually indicate its site. This site is oftenest in the upper lobe—according to Weil four times out of five—and also oftenest along its anterior margins, or in the axillary line. Around it there is generally a thicker deposit of fibrin than elsewhere. On section the lung is

found full of blood and atelectatic. It contains absolutely no air; what is left after compression is rapidly absorbed, a process which is often complete one to two hours from the time of perforation (Wintrich, Traube). Of the tuberculous and other processes which may be found in the lungs on both sides, no description need here be given.

The tension of the contained air has been tested by Homolle, Powell, Leyden, Weil, and others, and found to vary within very wide limits, from markedly positive to equally marked negative pressure. This difference depends wholly on the character of the perforation—whether open, closed, or valvular. A pneumothorax is said to be open as long as there is perfectly free entrance and exit of air; intrapleural tension is then practically that of the atmosphere. On the other hand, a closed pneumothorax is one in which the original perforation has become wholly occluded so that with neither inspiration nor expiration does it permit the passage of air. Such closure may be effected by immediate cicatrization, or by a slower process under the favoring influence of an effusion, or by a false membane; it is not necessarily permanent. Intrapleural tension in closed pneumothorax may, at the moment of occlusion, be anything from atmospheric to highly positive; later it diminishes as the air becomes absorbed, and eventually becomes increasingly negative. Closed pneumothorax is infrequent, even months after the onset. Weil found it only seven times in thirty-three cases. The usual form of pneumothorax, especially in tuberculous cases, is the valvular; the perforation being of such a character that it opens only at certain phases of respiration and closes at others. The explanation usually given is that with expiratory retraction the tortuous fistula closes, or the lips fall together, or a bit of false membrane at the orifice forms an actual valve; hence with each inspiration air is sucked into the pleura, which cannot escape with expiration, and thus a high degree of tension is soon reached. The objections to this theory are, as perceived by Behier, first, that the affected side is already in permanent inspiratory position, and practically takes no further part in respiration; and second, that, even if it did so, as soon as the intrapleural pressure at the end of inspiration exceeds the intrapulmonary, it is difficult to understand how still more air could possibly be pumped in. Bouveret makes the much more plausible suggestion that in valvular pneumothorax it is by expiratory efforts, chiefly cough, that an excess of air is forced into the pleura. The perforation gives way to the force from within the lung, but closes as soon as the latter ceases, the closure being further maintained by the constantly increasing excess of intrapleural tension. It seems to me probable

that while, after a pneumothorax is once established, a slight additional amount of air may be pumped in by inspiration, all extreme cases can be accounted for only by the expiratory theory of Bouveret.

The composition of the air contained in the pleural cavity has been subjected to several analyses, first by Davy, later by Wintrich, Demarquay and Leconte, and Ewald, more recently by Rodet and Pourrat. The sum of these observations is that in open pneumothorax the air differs but little in composition from the external atmosphere, containing oxygen, nitrogen, and carbonic acid. If, however, the pneumothorax become closed, the oxygen steadily diminishes and the carbonic dioxide increases; in pneumopyothorax the proportion of the latter may be as high as forty-nine per cent. (Hoppe-Seyler). In putrid cases there is also a certain quantity of sulphuretted hydrogen. Ewald has suggested the use of such analysis to determine the nature of the opening. He claims that if there is less than five per cent. of carbonic acid, the perforation is probably open; if from five to ten per cent., it is partly open, *i.e.*, valvular; if over ten per cent., it is absolutely closed.

The pleuritic exudate usually found in connection with pneumothorax may be either serofibrinous or purulent. It was formerly supposed that pneumohydrothorax was infrequent, and that pus was the rule. Senator in 1880 called especial attention to the frequency of the serofibrinous form, and since then his observations have been generally confirmed. Weil met with only eleven purulent cases out of twenty-eight. Of Netter's fifteen cases only three were purulent. It seems therefore that the serofibrinous is much the more frequent form of the two. Putridity is rare.

The displacement of heart, mediastinum, and diaphragm found in pneumothorax must, of course, depend somewhat upon the degree of intrapleural tension, though not so much as might at first thought appear. Both Powell and Weil have shown by experiment that even in open pneumothorax, where simply atmospheric pressure prevails in the pleural cavity, the degree of displacement is very great. It is not necessary to repeat here the explanation of this fact, already given in the section on the pathology of pleurisy. It was there seen that the displacement of the thoracic organs is more a question of relative than of absolute tension. If the pressure in one pleural cavity is *nil*, and in the other suddenly rises to 15 mm. of mercury, the heart and mediastinum must evidently move towards the vacuum. So with the lung and diaphragm; normally held in a state of tension by the negative pressure of the pleural cavity, they must relax the moment this negative pressure is replaced by that of even a minimum quantity of air. It is easy, therefore, to understand why an intrapleural pres-

sure equal to that of the external atmosphere should cause marked displacement. Extreme degrees are found only with the valvular form. The diaphragm may even curve downwards, pushing before it both spleen and liver; the latter organ may lie quite outside the thorax, and, according to Weil, may be tilted so that the left lobe is higher than the right. The heart, in left pneumothorax, may lie wholly to the right of the median line, and the mediastinum a couple of inches beyond the border of the sternum. Here, as in effusion, the heart is but slightly rotated; its apex maintains nearly the same position relative to the base as before. That there may be a very considerable bending and occlusion of the inferior vena cava has been demonstrated by the direct observations of Bartels and Fraentzel in effusion, as well as by the experimental results of Rosenbach in artificial pneumothorax.

Pneumothorax is usually total; of Weil's thirty-six cases all but four involved the whole pleural cavity. A partial or circumscribed pneumothorax may occur where there are old adhesions; it is found oftenest at the base of the chest, though its presence in other situations, even at the apex, is possible. Double pneumothorax is exceedingly rare.

Symptoms.

A typical case of pneumothorax presents an extremely characteristic complex of symptoms. The onset is brusque and violent. The patient, usually a consumptive, more rarely an individual in apparently good health, is suddenly seized with an intolerable pain in the side. His face expresses great anxiety, even anguish; it may be pale and clammy, with blueness of the visible mucosæ, or more distinctly cyanotic. He can speak with difficulty, or the voice may be entirely lost. Violent paroxysms of cough often add to his distress. His extremities are cold, the temperature is often subnormal, the pulse is rapid and small, and the general condition is one of imminent collapse. The position assumed is characteristic: the patient either sits upon the edge of the bed, slightly bent, and supporting himself with rigid arms, or he lies semi-recumbent with knees drawn up, and partly rotated towards the unaffected side; this latter position was observed in all but two of Weil's cases. Exceptionally pneumothorax may produce immediate unconsciousness (case of Klemperer).

If, as usually happens, the immediate effects of such an attack are survived, the violence of the symptoms soon abates. In two to three days the pain and dyspnœa are considerably relieved, and the temperature returns to its former height, or even higher as a result of the complicating pleuritis. But this improvement is too often

only relative; the course of the pulmonary disease is rarely modified by this complication, and the patient gradually succumbs in the course of the next few weeks to progressive exhaustion.

Most cases of pneumothorax have the sudden onset above described. The initial symptoms may be less stormy, but there is usually at least a definite exacerbation of pain and dyspnœa. Weil remarks upon the astonishing accuracy with which most patients with pneumothorax can state the exact moment of perforation. But there are exceptions to this rule, and they are frequent enough to necessitate great caution in diagnosis. Especially is it true that the onset of a partial pneumothorax may be quite unnoticed. Even a total pneumothorax in a debilitated subject whose respiratory centres are already accustomed to a deficiency of oxygen, may be wholly latent in its development, as is frequently seen in the terminal stage of pulmonary phthisis. Here a physical examination alone will discover the true condition. The same may be said as to the development of effusion which in the presence of such marked respiratory symptoms as usually attend both pulmonary phthisis and pneumothorax will often fail to cause any notable change in the rational signs.

Physical Signs.

It is doubtful if there is any disease which gives rise to more pronounced and typical local signs than a general pneumothorax.

On *inspection* one is immediately struck with the almost total respiratory immobility of the affected side. This side also appears to be very considerably distended, a fact which may be demonstrated by mensuration, and the intercostal spaces are seen to be obliterated or even bulging. The heart's impulse may be visible in the left axilla, or to the right of the median line. The respiratory movement of the opposite lung is much exaggerated.

Palpation discloses in many cases an increased elasticity of the intercostal spaces; when this is marked intrapleural tension is probably high, and the perforation is valvular. Vocal fremitus is greatly diminished or entirely absent. The position of the heart's impulse, which in left pneumothorax is usually most marked over the lower part of the sternum, and that of the lower border of the liver and spleen, indicate the frequently enormous dislocation of the diaphragm and mediastinum; the whole liver may be found below the free border of the ribs.

Percussion on the affected side gives, as a rule, a loud non-tympanitic note of low pitch. Many authors describe this resonance as usually tympanitic; but Weil states that he has never yet met

with tympany in a single case, and my own experience coincides in the main with his. Theoretically, too, we should hardly expect a tympanitic resonance over a cavity with such rigid walls and filled with air under high tension. The pitch, however, is not always low. It must necessarily rise with any increase of intrapleural tension, and when this is very great the pitch may be so high as to approach actual flatness. Such instances are referred to by Osler and Walshe, but they must be very unusual in other than the partial forms. Though not tympanitic, the resonance of pneumothorax is, as a rule, easy to differentiate from that of the opposite side, and it is found to extend in every direction far beyond the normal boundaries of the lungs; thus it may even reach the margin of the ribs and the parasternal line of the opposite side. Over the upper part of the back and close to the spine there is often a small area of dulness if the compressed lung is in apposition to the chest.

The præcordia is, in right-sided pneumothorax, simply displaced bodily to the left; in left pneumothorax, its usual site is wholly resonant, and an area of dulness similar to the normal is found upon the right side between the fourth and sixth ribs. These changes, as well as those of the liver and spleen, do not differ in the main from those already described among the physical signs of pleuritic effusion. Here also, as in effusion, there is some retraction of the well lung, with resulting skodaic tympany. The diaphragm on the sound side is slightly depressed.

Auscultatory signs are varied and of exceptional value. The most characteristic condition is a great diminution or absolute cessation of all respiratory and vocal sounds over the lower and lateral regions of the chest. As the lung is approached a distant bronchial respiration may begin to be perceptible, although even here the silence may be absolute. Almost equally typical is a universal amphoric quality of transmitted sounds. Oftenest it is the respiration which first attracts attention as a low and distant musical puff. Very often a sound like the far off tinkling of a bell suddenly surprises the ear, a sound which may be imitated by dropping bits of sand into an empty glass. It is very doubtful whether this so-called metallic tinkle is due, as was supposed by Laennec, to the dripping of fluid, or whether the presence of fluid is even necessary for its production. Skoda was the first to claim that such a tinkle might originate in simple pneumothorax, without fluid, and even without open perforation; and Behier, by experiment, has demonstrated the accuracy of Skoda's view. It appears that any slight noise, like the bursting of a bubble or a râle, acquires a musical or tinkling quality by transmission through a chamber full of air. The origin of such sounds

in and upon the surface of the lung is not difficult to conceive. Besides respiration and the tinkle, all other sounds may have an amphoric quality, the voice, whisper, cough, and rarely even the sounds of the heart.

A peculiar sign of pneumothorax and one of the most characteristic is obtained by auscultatory percussion. While the stethoscope is applied, for example, to the front of the chest, strong percussion is made behind upon a coin or upon any indifferent substance as a plessimeter (Fraentzel). The sound thus produced has a marked metallic quality, and was termed by Trousseau *bruit d'arain.* Rarely this same sound may be heard on ordinary percussion.

In certain cases a loud amphoric blowing sound is heard with both inspiration and expiration, like that produced by the passage of air through an external fistula. It has a sort of metallic quality, and is followed by an amphoric echo. Weil considers it a measurably good sign of an open perforation.

Effusion probably begins as a rule very soon after perforation. In a case of Weil's it began within an hour. Its detection, however, is usually later, somewhere from the second to the fifth day; and the first sign which makes such detection possible is known as succussion. This is a splashing sound like that produced by shaking a large bottle partly filled with fluid, except that its quality may be decidedly amphoric. It can sometimes be heard at a considerable distance, or even by the patient himself. Usually it must be elicited by giving the patient a rather vigorous shake, while the ear is held to the chest. It appears long before there is a sufficient quantity of fluid to cause any flatness on percussion, and, on the other hand, as the chest fills it becomes less easily evoked and finally ceases.

When the fluid has reached a very considerable quantity, larger undoubtedly than is necessary in simple effusion, it gives evidence of its presence by the same physical signs as does the latter. These signs, however, present two very important points of difference in the two affections. In effusion, as we have seen, the fluid is not free to assume a hydrostatic level, but is compelled to adapt itself to the shape of the retracted lung, and hence the upper border of flatness is not a horizontal line, but a curve which varies constantly with the amount of fluid. When, on the contrary, fluid collects in the cavity of a pneumothorax it is no longer impeded by the lung, either in assuming its natural level or in constantly shifting its position with every change in that of the patient. This fact involves two very important consequences: first, the upper level of the fluid as obtained by percussion is invariably a horizontal line; and second, the position of the flat area varies inevitably with that of the patient. If, for

example, percussion is made when the patient is upright, the lower half of the chest may be perfectly flat; if now he is asked to lean far forward, or, still better, to lie upon the face, the area of flatness will be found to have given place to one of full non-tympanitic resonance.

The signs of partial pneumothorax do not differ from those described except in degree. Over a circumscribed area, generally at the base, there is diminished respiratory fremitus with possibly amphoric timbre. But any marked displacement of organs is lacking, and here especially the percussion note is much more apt to be dull than in the typical form. It is not surprising therefore that partial pneumothorax, occurring, as it does, oftenest in cases of advanced tuberculosis and with but little general disturbance, should be very frequently overlooked, or mistaken for other conditions.

Complications.

With the exception of the acute pleural inflammation which is almost a part of the disease itself, pneumothorax has but few and infrequent complications. Pleurisy of the opposite side seems to occur rather oftener than can be explained by simple coincidence (Senator). Subcutaneous emphysema may rarely accompany pneumothorax when the latter has originated in rupture of the œsophagus or has followed tracheotomy. Œdema of the opposite lung, or other causes of sudden death may develop here as in effusion, when the heart and great vessels are so compressed that an adequate compensation is impossible.

Diagnosis.

Often it is possible from the very attitude of the patient, and especially when in a phthisical individual a history of sudden pain and dyspnœa is obtained, to be at once measurably certain that a pneumothorax has developed. In other cases the symptoms are such as to arouse but little suspicion. In either case the only safe guide is physical examination; and the physician who does not examine his phthisical cases frequently and carefully will fail to recognize many a case of partial or even of general pneumothorax.

By the aid of the physical signs the diagnosis of a typical case is extremely easy. Extension of resonance beyond the normal boundaries of the lung, greatly diminished or absent respiration over this resonant area, and the marked displacement of mediastinum and diaphragm—these are the signs which, when thus combined, furnish irrefutable evidence of pneumothorax. Too much stress is usually laid upon tympanitic resonance and amphoric sounds. The former

is rarely present, the latter in not more than half the cases; neither adds much to the certainty of diagnosis.

Among the conditions most likely to be mistaken for pneumothorax is a unilateral emphysema. An instance in which such a case presented a remarkable similarity to pneumothorax has come under my own observation. The right lung was fibroid, and its contraction had drawn the heart a considerable distance to the right of the sternum. The left lung was in a state of vicarious emphysema; its borders extended much beyond their normal situation, both downwards and to the right, and resonance was everywhere exaggerated, almost tympanitic. The only differential sign—and this was conclusive—was the presence of a fairly good, though somewhat diminished, respiratory murmur. Such cases are undoubtedly exceptional, and yet it is not safe to depend upon the usual statement that emphysema is always bilateral.

Under the somewhat misleading name of *pyopneumothorax subphrenicus* an affection was first described by Leyden in 1880 which may bear a very close clinical resemblance to genuine pneumothorax. It consists in a collection of pus and air beneath the diaphragm, the result of a perforating ulcer of the stomach or duodenum, or of some other destructive process connected with the gastrointestinal tract. It does not appear to be so very infrequent, since Leyden in 1892 had already collected thirty-five cases. The peculiar clinical feature of these abscesses is that they may crowd up the diaphragm as high even as the second rib, and thus produce an area of flatness or tympanitic resonance (according to the patient's position) which involves nearly the whole half of the chest, while the abdomen perhaps appears to be quite normal. Points in favor of the subphrenic affection are the following: History of an abdominal trouble; good vesicular respiration over the retracted lung, which is not of course crowded inwards towards the spine as in pneumothorax, but simply rides upon the diaphragm and hence remains in apposition with the outer wall everywhere above the horizontal line of the abscess; a greater displacement of the liver, when the affection is on the right side, and much less displacement of the heart than would occur in pneumothorax. Succussion may be heard in both affections.

That a typical pneumothorax could be mistaken for a pulmonary cavity would be hardly possible on other than the most superficial examination. Cavities produce a retraction instead of distention of the chest, and the heart, if displaced at all, is drawn towards the affected side. But if a pneumothorax is circumscribed, or if it has resulted from an empyema, the diagnosis may be difficult; evacuation by vomica may have resulted in a pneumothorax and at the same time

in a contraction of the chest and displacement of the heart towards the affected side. Here as in partial pneumothorax there may be, if the perforation opens widely into a bronchus, transmission of the whispered voice, and exceptionally Wintrich's tone variation on percussion—a change in the pitch of tympany according as the mouth is open or closed. These signs are quite the same as in a large cavity, and in both also amphoric quality of transmitted sounds may be pronounced. An absolute diagnosis can hardly be made unless one is very familiar with the case, and with antecedent events.

Still greater is the possibility of mistaking a partial pneumothorax at the extreme base behind for a small effusion. It may give rise to almost absolute flatness, and to a curve which is very similar to that of a small collection of fluid. On auscultation also, both fremitus and respiration are found to be diminished or absent, or the latter may be bronchial. In two cases of this rare condition which I have recently seen, the following differential points were noted: The boundary of the flat area was not so sharply defined as in effusion; there was transmission of the whispered voice; and, most conclusive of all, while the exploratory needle evidently entered a cavity, repeated attempts failed to withdraw fluid. In a phthisical subject, signs of effusion at a posterior base should always suggest the possibility of partial pneumothorax.

Diaphragmatic hernia is another very rare condition which may resemble pneumothorax. It is hardly necessary to call attention to the slight tympanitic resonance with metallic tinkling and possibly succussion heard in the left axilla; these signs are transmitted from a distended stomach.

Whether a pneumothorax is open, closed, or valvular cannot, as a rule, be definitely determined by ordinary physical signs. Percussion is of little assistance. We have already seen that even in the open form resulting displacement of organs is very pronounced, and the heart may be wholly to the right of the median line. Any such excess as would demonstrate a high intrapleural tension would be very difficult to determine; and, moreover, the nature of the closure, whether permanent or valvular, would still be undecided. Auscultatory signs are sometimes of more assistance. Absolute silence over the whole chest is generally conceded to be a fairly good proof that the perforation is at least temporarily closed. On the other hand, a loud amphoric swashing sound with both inspiration and expiration, such as is heard at the external opening of an operated empyema, indicates open perforation. Further than this it is difficult to go without the aid of gas analyses, or manometric tests.

The *diagnosis of secondary effusion* is attended with no difficulty if

only sufficient fluid is present to give succussion, and, on the other hand, if the chest does not become so full that the presence of air can no longer be recognized; in the latter event the physical signs are precisely those of uncomplicated effusion and the history is the only clew to a primary pneumothorax. As long as the quantity of fluid is only moderate there is no excuse for the mistake, so often made, of diagnosticating a simple pleurisy. The fact that the line of flatness does not vary a hair from the level of the horizon ought to at once attract attention. It is then easy to determine the change of the fluid level on change of posture—a sign which is all the more noticeable because the change occurs with striking rapidity, and also because the line of effusion, being represented here by an abrupt transition from flatness to the full tone of pneumothorax, is extremely easy to percuss. These signs will lead to the test for succussion which, however, is now scarcely needed to confirm the diagnosis. As to the nature of the fluid, whether serum or pus, the signs here are the same, and often just as obscure, as in simple pleurisy. A daily hectic may be entirely wanting in suppuration, and if present it is often impossible to decide as to whether its origin is pleural or pulmonary. Exploratory puncture is the only safe test.

Course and Prognosis.

Tuberculous pneumothorax is an extremely grave affection, both because of the primary tuberculosis and from the nature of the accident itself. Immediate death—in the first few hours—is exceptional. It occurred in only 5 of 51 cases collected by Saussier; and Weil also states that the very great majority of his patients recovered from the primary attack. But more than half of all cases die during the first month (50 per cent., Weil; 58 per cent., Saussier), and an ultimate complete recovery is extremely rare. Of Weil's 46 cases all but 2 died; although in 10 the course of the disease is described as long and benignant.

In rapidly fatal cases the patient never recovers from the primary collapse. His face, at first cyanotic, soon becomes of a dusky pallor; the sensorium is clouded; the rapid respiration is interrupted only by occasional paroxysms of cough, which are followed by attacks of threatening suffocation; the pulse grows more and more rapid and imperceptible, and death finally occurs from asphyxia and circulatory insufficiency. Rosenbach, in experiments upon blood pressure in artificial pneumothorax, found that although from venous obstruction and other causes the volume of arterial blood is much diminished, the pressure is at first maintained by increased action of

the heart and by arterial contraction; as soon, however, as pressure begins to fall, death is imminent. Most cases of pneumothorax which are so rapidly fatal are probably valvular; Bouveret calls this the suffocative form.

As a rule, the onset of pneumothorax is survived, and after two to three days the violence of both pain and dyspnœa abates. Death from asphyxia is still possible during the next ten days. But usually the prognosis from now on will depend almost wholly on the character and stage of the primary tuberculosis. It is only when the lungs are but moderately involved, when the patient's strength and general nutrition are good, and when the daily temperature has kept at a low range that life will be prolonged for more than one or two months. More than half of all cases, as we have just seen, die within thirty days from cachexia and exhaustion.

As to the pneumothorax and resulting effusion, there are several possibilities. The pleuritic inflammation generally adds somewhat to the already existing fever, and indeed a rather marked febrile reaction with the onset of pleurisy is to be regarded as on the whole a favorable sign (Weil). If later, after ten to fourteen days, the temperature falls and only a moderate quantity of serofibrinous or seropurulent exudate has developed, the case may be regarded as progressing favorably. The pneumohydrothorax may then remain unchanged until, after months or occasionally years, death occurs from tuberculosis; or, in rare instances, both air and serum may be absorbed. With purulent effusion the outlook is of course more grave. But even here the character of the empyema is often benign, there may be little or no fever, and life is sometimes indefinitely prolonged.

Double pneumothorax is an extremely rare occurrence, and is usually fatal within a few hours or days at most. Putridity is also a condition of great gravity, though at least temporary recovery is not impossible. Partial pneumothorax is the mildest form of all, and unless there is suppuration does not usually alter in any way the course of the primary disease.

The prognosis of *non-tuberculous pneumothorax* depends also upon that of the primary disease; the latter is occasionally such as to preclude recovery, as may be seen by referring to the section on etiology. If this is not the case, as in the traumatic and especially in the so-called "accidental" form, the prospect of complete recovery is exceedingly good. An exception is to be made of the very rare cases which result from chronic emphysema; of 12 such cases collected by Gaillard, 8 were fatal. But in the usual form, that of young adults, not only is the outcome almost always favorable—34

out of 37 cases of Gaillard—but the course of the affection is extremely short and mild; in 22 of Gaillard's cases there was no effusion, and often there was no rise of temperature. The average duration from the date of onset to complete resorption is a month; in some cases without pleurisy there is complete recovery in ten days; in others, especially when effusion has supervened (Gaillard) two months may elapse before the normal conditions in the chest are entirely restored.

Treatment.

At the onset of pneumothorax, opium is an indispensable and most salutary remedy. It not only relieves the agonizing pain and dyspnœa, it also controls cough; and if it is true that cough is the main factor in producing the excessive tension of the suffocative forms, the administration of this drug may actually save life. Here, as in pleurisy, the subcutaneous injection of morphine is an invaluable method, because, if necessary, it can be safely repeated at short intervals until the desired effect is obtained. In milder cases, in which pain is not prominent, the relief of cough may be as well if not even better effected by the subcutaneous injection, in half-grain doses, of phosphate of codeine. The local application of dry cups, hot fomentations, or poultices, will also give some relief. Threatened diminution of arterial pressure and collapse must be met by stimulants and by heat to the extremities. In a case reported by Vickery, the inhalation of oxygen appeared to be of great service.

The *operative* treatment of pneumothorax must depend upon the indication which it is designed to meet.

1. The *indicatio vitalis* may demand the immediate relief of intrapleural tension when life is seriously threatened from suffocation. The chances of successful interference can be estimated correctly only when the conditions which govern this intrapleural tension are borne in mind. In the first place, it is to be remembered that in the first few days at least—the period of greatest danger—every pneumothorax is either open or valvular. In an open pneumothorax it is plain that no relief can possibly be given by operation. Air enters from within as fast as it is removed from without. In a valvular pneumothorax, however, the more common form in tuberculosis, conditions are different; the contained air is under considerable tension, and aspiration or even puncture may give immediate relief. But, as a rule, this relief is only temporary; the following respiration or the first paroxysm of cough again opens the valve, and very soon intrapleural pressure is as high as before. Perhaps in some cases this process is slower than in others, or possibly the artificial repression

of cough may sometimes retard very considerably the recurrence of overdistention; otherwise it is difficult to explain the good results which have occasionally followed aspiration. Macqret, for example, affirms that it always gives relief. But such an experience is exceptional; and theoretically, also, it is quite evident that permanent relief can be expected only from a permanent opening, such as will constantly maintain an atmospheric pressure within the pleural cavity. Wintrich, Biermer, and Unverricht advise, therefore, that after puncture the cannula be allowed to remain. Bouveret makes a still better suggestion: he recommends the use of a small trocar and cannula, 4 cm. in length and 3 mm. in diameter, and provided with two lateral rings for attachment to the chest. This trocar is inserted under aseptic precautions, and the cannula is allowed to remain beneath a thick surgical dressing.

It would appear, then, that when suffocation is threatened, the air may first be aspirated as is commonly done in effusion; if this gives only temporary relief, a cannula *à demeure* should be introduced.

2. The *removal of serum* by aspiration may be indicated after a period of at least six weeks has elapsed from the onset of a pneumohydrothorax (Weil). Earlier than this the perforation is likely to be still open, or at least so imperfectly closed that any negative pleural pressure would be apt to open it afresh. Hence, during the first six weeks, the *indicatio vitalis*, when the quantity of fluid is so excessive as to endanger life, is the only condition which warrants aspiration (Weil). Later, any considerable quantity of serum which has remained stationary for some time and shows no tendency to spontaneous absorption, may be withdrawn with advantage in the same way as in simple pleurisy.

If the amount of fluid is small in proportion to that of the air, it is, perhaps, questionable whether the aspiration of the latter, under the above conditions as to time, may not be more in accord with nature's method than the removal of the fluid. Weil believes that it is the air of which spontaneous absorption is most difficult; and, indeed, in cases of recovery, the process often seems to be first expulsion of air by the fluid, and then absorption of the latter. Weil, therefore, recommends aspiration of 400–1,000 c.c. of air when its quantity greatly exceeds that of the fluid. In some cases of larger effusion, it may be advisable to remove a small quantity of each.

3. The *removal of pus* in a case of tuberculous pneumopyothorax is a procedure about which there is much difference of opinion, not only as to the most suitable method but even as to the advisability of any interference at all. In traumatic forms, or when a pneumothorax has resulted from an empyema, there can, of course, be no question as

to the necessity of the radical operation. But in the tuberculous cases, as in the more common forms of tuberculous empyema, the results of operation are frequently discouraging. Especially when it is considered that such individuals are often afebrile, and sometimes carry their pus about for years without notable deterioration of the general health, there is but little temptation to do a radical operation, with all its possibilities of chronic fistula, amyloid degeneration, putridity, and rapid decline. On the other hand, operated cases may recover completely. Leyden, for instance, operated on four cases of pneumopyothorax, two of which still lived at an interval of one and two and one-half years respectively; both had fistulæ, but were in fair health. Leyden thinks that operation prolongs life. Bohland would treat by repeated puncture or by the method of Bülau. Merklen advises pleurotomy when the affection is recent and when the pulmonary lesions are slight; he states that Rendu has operated twice, with the result that while one patient died immediately after operation, the second showed a marked amelioration and lived for six months. If after repeated aspiration there is recurrence, he would incise. He believes that in many cases life may thus be saved. Fraentzel, Senator, and Goldamner are all against thoracotomy. Netter favors it unconditionally in all cases, on the ground that, besides the bacillus tuberculosis, the pus of pneumopyothorax always contains both pyogenic and saprogenic germs.

These great differences of opinion may be taken as proof that no universal rule can be formulated for the treatment of pneumopyothorax. Here, if anywhere in medicine, there is need of sharp individualization. In at least two conditions, it seems to me that the radical operation should be unhesitatingly advised: First, in a comparatively well-nourished individual, with but slight pulmonary involvement, in whom a daily hectic is slowly but surely undermining the strength. These cases are susceptible of complete recovery in such a climate, for example, as that of Colorado, and should have the benefit of the doubt. Resection would here be the preferable operation. Second, in any case, no matter how far advanced, when the constant discharge of large quantities of pus by vomica renders the condition of the patient so deplorable that relief must be sought at all hazards. It would be best here simply to incise. On the other hand, either aspiration or the method of Bülau would seem to me the operation of choice: First, in a chronic and incurable case of phthisis, with considerable emaciation and pulmonary cavities, in which the presence of but little fever makes it quite possible that life may be indefinitely prolonged; second, in the last stages of phthisis, in answer to the *indicatio vitalis*. In either case aspiration should be repeated

as often as the effusion becomes more than simply moderate. These indications are not given here as rules of conduct, but as hints suggested by my own experience and that of others. The individual case will always remain a problem in itself, which the above suggestions will only help to solve.

It remains to consider the treatment of one or two special varieties of pneumothorax. In the partial form the expectant plan is usually all that is required; in case of suppuration the same indications will arise as in the typical disease. Accidental pneumothorax, occurring in an apparently healthy individual, will at first demand the same treatment for pain, dyspnœa, and possibly also suffocation, as the tuberculous forms. When after two to three days the acuteness of these symptoms has subsided, the patient may feel inclined to get about, since the fever and other symptoms of secondary pleuritis are usually wanting. This should be positively forbidden. The chief indication is to aid in every way in effecting an early closure of the perforation, and to this end complete bodily rest is the first essential. Cough, if present should be restrained by morphine or codeine. Under such management recovery in these cases is usually rapid, and any subsequent operative interference is rarely indicated.

HÆMOTHORAX.

Definition.—The accumulation of pure blood in the pleural cavity.

Etiology.

Hæmothorax is always a secondary condition. Except as a result of trauma it is exceedingly rare, occasional instances having occurred from rupture of an aneurysm, ulceration of the aorta, or bleeding from the venæ cavæ. In a case reported by Wintrich hemorrhage was caused by caries of a rib, with resulting erosion of an intercostal artery. Among traumatic causes are penetrating wounds, severe contusions of the lung, and injury of the intercostal artery from operation.

Pathological Anatomy.

The condition of the lung and the displacement of organs present no important variations from those of ordinary effusion.

The question of chief interest relates to the changes which take place in the blood itself. These have been studied experimentally by Penzoldt and Wintrich, and more recently by Pagenstecher. The results obtained by the latter, from the injection of fresh blood into

the pleural cavity of animals, were the following: 1. Two hours from the time of injection the blood was still uncoagulated; in six hours it had changed to a fluid containing a few clots and resembling blood, but not susceptible of further coagulation. Pagenstecher concludes, therefore, that the pleura has, to a certain degree, the power of preventing coagulation. These results appear to be at variance with those of Penzoldt, who found that although the pleura seems to retard coagulation, this process was invariably complete in twenty-four hours at the most. 2. The blood is rapidly and completely absorbed from the pleural cavity, without residua other than those left by the clots. These are converted into fibrous tissue by exactly the same process as that concerned in the organization of a thrombus. 3. Blood alone does not give rise to pleural inflammation; the latter may, however, often result from the same cause as the hemorrhage.

Symptoms.

Certain forms of pleural hemorrhage—as, for example, aortic rupture—must of necessity prove immediately fatal. Otherwise copious hemorrhage is announced by sudden intense pain, which is rapidly followed by the symptoms of acute anæmia, viz., rapid and feeble pulse, pallor, coldness of the extremities, and sometimes complete syncope. Dyspnœa is also extreme if the hemorrhage is large, and later the condition may be complicated by the development of acute pleuritis, the effusion of which may add to the intrapleural pressure; here, as in the rarer cases of putrid decomposition of the clot, infection has resulted from the primary lesion. When the development of the hemorrhage is more gradual, the pain and dyspnœa are also less sudden and severe. The physical signs of hæmothorax are identical with those of simple effusion.

Diagnosis.

The diagnosis of hæmothorax can usually be made from the physical signs of fluid in the chest, in conjunction either with acute anæmia or with an adequate known cause of hemorrhage. The source of the blood is more difficult to determine. Even in traumatic cases with external wound, it is often impossible to tell whether it comes from an intercostal artery or from the lung. The latter is oftenest the case, and may be considered certain if there is bloody sputum. Even when there is no hæmoptysis, the hemorrhage is most probably from the lung, unless the mammary or intercostal artery is actually found bleeding in the wound.

Prognosis.

The prognosis of pleural hemorrhage is almost entirely dependent upon the primary lesion and the probability of infection. In general, the immediate danger to life is very great, and hemorrhage from an artery of any size is apt to prove rapidly fatal. Or, if the first few hours are survived, the risk of compression is still considerable, either from further hemorrhage, from pneumothorax, or from pleuritic effusion. When these dangers have been safely passed, the ultimate complete absorption of the hæmothorax may be confidently expected.

Treatment.

The first and most immediate indication is to check the hemorrhage. Absolute rest, ice bags to the chest and possibly also to the scrotum, morphine in sufficient quantity to prevent cough, a light and non-stimulating diet—these are the measures most likely to be of service. Once developed, an uncomplicated hæmothorax should in most cases be let alone. Any attempt to remove the blood would certainly be attended with some danger of recurrence, and at best merely hasten what nature can better accomplish by safer means. If, however, the quantity of fluid is great, the *indicatio vitalis* may demand interference. The attempt should then be made to remove by simple aspiration just enough of the fluid blood to give relief. If this proves unsuccessful, and the presence of clots makes aspiration impossible, the radical operation should be performed and a limited quantity of coagula removed. It is again to be emphasized that, on account of the danger of recurrence, neither of these operations should be resorted to except as a final necessity.

HYDROTHORAX.

The simple transudation of serum into the pleural cavity is almost invariably associated with general anasarca. It is, therefore, secondary to such dropsical affections as those of the heart and kidneys and profound anæmia. It may exceptionally result from local venous stasis in the pleura, due either to pressure of a new growth or to thrombosis of the azygos; a case of the latter is reported by White, in which, in the course of six days, two hundred and ninety-six ounces of serum were aspirated from the right pleural cavity. As a rule, the condition is bilateral, though the quantity of fluid may be somewhat greater on the side upon which the patient habitually lies.

The fluid of hydrothorax is precisely similar to blood serum. It contains, of course, no fibrin and no cellular elements. The pleural walls are somewhat swollen and boggy, and have lost something of their normal gloss. The lower portions of the lung are markedly œdematous. The phenomena of compression do not differ from those accompanying pleuritic effusion, except in so far as they are modified by the bilateral character of the transudate and its frequent association with ascites.

Symptoms referable to hydrothorax are simply those of compression. The physical signs are in the main those of effusion; the fluid probably takes the same shape and has the same contour as in the latter; but, owing to the complicating œdema of the lung and the resulting dulness on percussion, its upper border is extremely difficult to define.

Diagnosis must depend on the bilateral condition, the absence of fever, and the general dropsy.

Prognosis and *treatment* are both mainly dependent upon the primary disease. If local symptoms are threatening, temporary relief may be afforded by aspiration.

ECHINOCOCCUS OF THE PLEURA.

The very great rarity of this affection may be estimated from the fact that Thomas, among 1,900 cases of hydatids, found only one per cent. involving the pleura alone. Of 983 cases investigated by Neisser, 17 were primary in the pleura. The proportion of secondary cases, nearly always of either pulmonary or hepatic origin, is somewhat greater. Maydl reports the results of operation on 29 cases of pleural hydatids; of these, 8 at least were known to be primary, and of the others 4 were secondary to hydatids of the lung, 11 to those of the liver, and the others were doubtful. The greater relative frequency of this disease in certain countries is well known.

Pathology.

Primary echinococcus of the pleura is usually solitary. The cyst may be situated in any part of the pleural cavity, and may reach the dimensions of a child's head. Its growth is usually inwards, and gives rise to atypical compression of the lung, and varying degrees of displacement of other organs. In certain instances, strange to say, its development is outwards, and causes a considerable degree of local bulging of the chest. The pleural cavity about the cyst is usually obliterated by dense adhesions. The cyst wall is composed

of a membrana propria, of laminated structure and peculiar to the echinococcus, and also of an adventitious membrane furnished by the pleura itself. This wall is of considerable thickness, and on incision its inner surface is often found to be rough and irregular. The cyst may contain either a clear non-albuminous fluid or pus. The latter is probably rare, except in cases of communication with the lung, when the cyst may also contain air. According to Neisser, daughter cysts are quite unusual. Secondary pleural hydatids originate oftenest in the liver, and are therefore most frequent at the base of the right chest. One or more separate cysts may develop in the same way as the primary one, or daughter cysts may have been discharged from the lung or liver into the free pleural cavity. This is followed in most cases by pleural suppuration, and not infrequently by pneumothorax.

Symptoms.

Severe pain in the side is said by Neisser to appear suddenly with the very beginning of the disease, and to persist quite constantly throughout its course. Later there is usually dyspnœa, which steadily increases with the growth of the cyst, so that decubitus upon the affected side is almost invariable. Fever is lacking in the primary uncomplicated forms, but there is, as a rule, a steady development of anæmia and emaciation. The *physical signs* are in the main identical with those of a solid growth or encapsulated effusion as long as the cyst is of moderate size, and its walls are intact; there is flatness on percussion, with diminished or absent voice, respiration, and fremitus, and possibly displacement of mediastinum and diaphragm. The external chest wall may show a decided local bulging, over which in some cases there is intercostal fluctuation. Hydatid fremitus has never been detected. Flatness over the whole side with great displacement of organs, and all the other signs of large effusion may be found when the cyst is enormous, or when the secondary rupture of a pulmonary or hepatic cyst has given rise to a general empyema; in other cases there may be the usual signs of pneumopyothorax.

Diagnosis.

The diagnosis of pleural hydatid is manifestly difficult, and the condition is almost invariably mistaken for effusion. An atypical area of flatness with the other signs ordinarily associated with fluid, especially in connection with a local bulging of the chest, should always lead to the suspicion of either circumscribed pleurisy, malignant growth, or hydatid. Exploratory puncture will then

eliminate cancer, and the character of the fluid must be further interrogated as to evidences of echinococcus. If it is clear and non-albuminous, the diagnosis of the latter may be regarded as assured; otherwise it must be searched for hooklets, and if these are not found, as is very often the case, an absolute conclusion cannot be reached. Evidences of pulmonary or hepatic echinococcus will then be especially valuable. This would also be the case where the signs are simply those of large effusion or pneumothorax. Here there would scarcely be any suspicion of hydatids unless aroused by purely extrapleural conditions, by suggestive elements in the patient's history, or by the escape of daughter cysts either by vomica or through the external opening after operation.

Prognosis.

The prognosis of this condition is very grave. Left to itself it is said to be inevitably fatal in from one and a half to four years, death resulting from suffocation or from a complicating pyothorax or pneumopyothorax. By timely operation life may often be saved if threatened solely by the intrapleural affection.

Treatment.

This must necessarily be operative; and two methods, simple aspiration and thoracotomy, have been tried. It seems from the statistics of Neisser and Maydl that the radical operation, preferably with resection, has given incomparably the best results. Neisser collected 16 cases which had been submitted to operation; 8 were simply punctured, and of these only 2 recovered; the other 8 were treated by thoracotomy with only 2 deaths. Maydl reports 29 operated cases; of 16 which were simply punctured, 11 died; while of 13 in which either incision or resection was performed only 3 died, and the rest fully recovered.

It seems, therefore, that aspiration is quite inadequate in the treatment of this disease, and that the radical operation is invariably indicated. This is the opinion of Maydl, Heydenreich, and Koenig; and these are also agreed that resection is always better than simple incision. The operation has here no special features; daughter cysts of very considerable size have been extracted through the opening, and in a case of Coupland's the fistula remained open until numerous shreds of membrane, evidently portions of the hydatid wall, were thus removed.

MALIGNANT NEW GROWTHS.

The pleural cavity may be the seat of either sarcoma or carcinoma; the latter is much the more frequent of the two, and in the following description it will be almost exclusively considered.

Pleural cancer is usually secondary. It is often associated with malignant disease of the lung as pleuropulmonary cancer, both being the result of extension from the breast, the axillary glands, the œsophagus, the thyroid, the stomach, or other abdominal organs. The existence of primary pleural cancer was formerly denied, but Wagner in 1876 first described a form under the name of endothelial cancer which has since been studied by Birch-Hirschfeld, Neelsen, and more recently by Fraenkel, and which may unquestionably originate in the pleura itself. It does not appear to be extremely rare, cases having been recently reported by Rossier, Harris (two cases), Hebb, and Brosch.

The pathological appearances in the secondary forms vary of course within wide limits. In some cases the growth appears upon the pleura as disseminated nodules, sometimes flattened, at other times prominent, which vary in size from a pea to a child's head. Or the pleural cavity may be directly invaded by a cancerous mass which has simply grown into it from a neighboring organ. In either case the growth, if large, may cause marked displacement; the lung retracts, the heart may be crowded to one side, and rarely there may be a local bulging of the chest wall.

The primary form above alluded to as endothelial cancer has some especially characteristic features. It is usually diffuse, and the whole pleura of one side is converted into a dense resisting layer, one-half to one, rarely two or even more centimetres in thickness (case of Hebb). It bears a much greater resemblance to ordinary fibroid thickening than to a new growth, and undoubtedly has often been mistaken for such. Its inner surface may be smooth, or markedly trabeculated like an hypertrophied bladder; adhesions may also exist between the opposite pleural surfaces. On section a few drops of a chylous fluid can often be expressed from the cut surface. Microscopically, this tissue is found to consist of a fibrous stroma in which are enlarged lymph spaces more or less completely filled with polymorphous cells. Although it is the opinion of most pathologists (for example, both Wagner and Ziegler) that this growth should be classed among the endothelial cancers, Fraenkel believes that it is inflammatory, probably infectious, and that a better name would be "lymphangitis prolifera." At all events, it has, as Fraen-

kel admits, all the clinical characteristics of malignancy. If this primary form has existed for any length of time, there will be found a marked contraction of the chest, especially of its lateral and posterior regions. The lung may be small and atelectatic, but otherwise wholly normal; or it may also contain secondary cancerous deposits.

Pleural cancer is generally accompanied by serofibrinous effusion which in one-half to two-thirds of all cases (Netter) is hemorrhagic. Fraentzel states that the fluid is usually a simple transudation; this seems very doubtful in view of the sudden pain and fever which often attend its development; and it is far more probable that it is usually an inflammatory exudate and the result of pleurisy.

Symptoms.

The onset of pleural cancer is usually insidious. There may be a constant dull pain in the side; and if the tumor reaches any considerable size it will in time give rise to dyspnœa. A growing cachexia, with progressive emaciation, loss of strength, and sallow or greenish-yellow hue of the skin, will often be the most noticeable indication of serious disease. In other cases the first evidence of the affection will be an acute attack of pleurisy; a sharp, sudden pain in the side is followed by fever, dyspnœa, and the rapid development of effusion. The latter, even when hemorrhagic, may not reform after aspiration, as in a case reported by Dutil; or, more frequently, there is obstinate recurrence up to the time of death.

On *physical examination* it will often be noticed that the axillary or cervical glands are considerably enlarged. Sometimes malignant disease elsewhere than in the chest may be discovered. Thoracic signs are inconstant and extremely varied. A large effusion may completely mask the underlying cause and, before aspiration, fail to suggest anything more than an ordinary pleurisy; this is probably the rule. After repeated punctures, however, there develops in certain cases, oftenest endothelial, marked deformity of the chest, especially noticeable in its lateral and posterior regions, and due to contraction of the diffuse pleural growth. The characteristic feature of this process is the extreme rapidity with which it takes place, far greater than in the usual forms of simple pleurisy. Respiration over the retracted side is usually bronchial (Fraenkel). In other cases the growth itself may give rise to pronounced signs of compression with circumscribed protrusion of the chest wall; over the tumor the percussion note is flat, sensation of resistance very marked, voice and respiration much diminished or absent. Fremitus may or may not be

preserved. The area over which these signs are found may, of course, present any conceivable shape, though hardly that of a typical pleuritic effusion.

Diagnosis.

The diagnosis of pleural cancer is often an impossibility. If there is no effusion, it must depend primarily upon the discovery in the chest of an area of flatness with diminished respiratory and vocal signs, which has an atypical shape and position. Combined with this there must be some general cachexia, with or without enlarged axillary or cervical glands, and possibly malignant disease elsewhere.

In the great majority of cases pleural cancer is first suspected on exploratory puncture or aspiration, a hemorrhagic exudate being usually indicative of either pleural tuberculosis or cancer. More or less certainty in favor of the latter can, however, be acquired only when the following conditions are combined:

1. A hemorrhagic effusion so rich in red blood corpuscles as to closely resemble pure blood. This deep red, often venous color, in distinction from the lighter shades usually found in tuberculosis, is quite characteristic of pleural cancer. At the same time it is to be remembered that not all cancerous effusions are hemorrhagic; Netter says only half or two-thirds of all cases.

2. The presence of considerable fat, either free as isolated globules, or contained in degenerated epithelial cells. The latter may be so full of fat as to present a distinctly mulberry appearance, quite like the cells which Quincke has described as somewhat characteristic of cancer. Free fat may in some cases be so abundant that the effusion is distinctly chyliform. The statement is often made that these chylous pleurisies are usually tuberculous; Quincke and Fraenkel both maintain that they are at least equally characteristic of cancer. Indeed, the study of chyliform effusions made by Bargebuhr would indicate that cancer is even a more frequent cause of this condition. Of ten cases, the origin of which could be traced, four were from cancer, four from simple pleurisy, one from pulmonary abscess, and one was tuberculous.

3. The discovery of small masses which have a distinctly cancerous structure. This is often possible when the process is destructive. Single or even agglomerated polymorphous cells are in no way distinctive, being associated with quite a number of other conditions.

The hemorrhagic fluid of cancerous pleurisy is extremely apt to recur after puncture; and if repeated aspiration is followed by the

rapid development of retraction and thoracic deformity, this in connection with the above peculiarities of the fluid will afford valuable evidence of malignancy.

As to the *prognosis* and *treatment* of this affection nothing need be said. The primary endothelial variety appears to be equally malignant with the more frequent secondary forms. The treatment can only be supporting, with repeated aspiration if the quantity of fluid becomes great, or gives rise to symptoms of distress.

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ASTHMA.

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ASTHMA.

INTRODUCTION.

With the names asthma, asthma bronchiale, asthma nervosum, asthma essentiale, asthma spasmodicum, we do not to-day connect the idea of a definite pathologico-anatomical process, but rather that of a sharply marked group of clinical symptoms the most striking of which are attacks of dyspnœa.

A definite statement as to the occurrence of a nervous or spasmodic asthma we meet with first in Van Helmont. But an accurate description of the features of the disease is still lacking. This we find first in Willis, whose treatment of the subject contributed essentially to procure a more general acceptance of the view as to the nervous nature of the disease. For a long time Willis' view of the spasmodic nature of asthma was the prevalent one. But gradually the conception of the word "asthma" became more widely extended, one spoke of asthma-like dyspnœa, and new forms of asthma were distinguished, so that finally the designation "asthma" was applied to all kinds of dyspnœic attacks. But this confusion did not last long. The rise of physical diagnosis and of pathological anatomy in this century had the result that more and more of the forms which hitherto had been classed with asthma nervosum were recognized as having an organic basis, and so the sphere of true asthma became constantly more contracted until finally the opposite extreme was reached. While formerly many forms of asthma, and of asthma-like affections were recognized, some now went so far as to deny absolutely the existence of an idiopathic asthma (Rostan, Bouillaud, Louis, and others). There was an interval before voices again began to be heard which contended for the existence of a genuine idiopathic asthma. It was especially Romberg who maintained the idiopathic and nervous nature of asthma with good physiological arguments, supported by the demonstration made by Reissersen of unstriped muscular fibres in the walls of the bronchioles; and Bergson and Salter, whose works contributed materially to the rehabilitation of asthma nervosum, soon followed him. Since then the

existence of idiopathic nervous asthma has been generally recognized; the battle is now confined to an essentially narrower field.

The question now is, not whether there is an idiopathic asthma, but, what is the especial mechanism of the asthmatic attack, how does such an attack originate, in what way is it brought to an end? There are three theories which have been proposed to explain asthmatic attacks. The oldest is the theory of spasm of the bronchial muscles which has found an enthusiastic and energetic defender in Biermer especially. According to this theory the phenomena of asthma are held to result from a spasm of the bronchioles.

To the theory of bronchial spasm another theory, that of a tonic spasm of the diaphragm, was opposed by Wintrich. This theory soon found adherents in Bamberger, Lehmann, and others.

A third theory is that vasomotor disturbances in the lesser circulation, the overfilling of the blood-vessels, and a swelling of the bronchial mucous membrane resulting therefrom are the causes of the impediment to respiration. This view has been especially supported by Weber and Stoerk, Glasgow, Clark, and others. These are the theories which now prevail. Yet not only are there still differences of opinion with respect to the theory of its causation, but there is also a great confusion in the interpretation of the symptoms of asthma, in that the various and in part widely different forms of disease which may lead to it are not sharply separated from each other, and that cause and effect are often not distinguished.

Definition.

First of all it must be clearly understood that the word "asthma" represents merely a collection of symptoms. If clearness is to obtain, we must start with a well-defined complexus of symptoms; we must first establish what that complexus of symptoms is which we call asthma. Only when a positive answer is given to this question, when we are clear as to the group of clinical symptoms which must be present when we speak of asthma, can we proceed to the solution of the second question, that of the etiology and mode of origin of the disease. If the literature is examined with reference to the first question, agreement as to the definition of asthma is by no means to be found.

All paroxysmal dyspnœa for the occurrence of which a sufficient pathological change cannot be demonstrated is called asthma by many. But this is, without doubt, too comprehensive a definition. A dyspnœa of sudden development and without corresponding organic changes is not sufficient to constitute asthma.

Asthma is an especial and peculiar form of paroxysmal dyspnœa, characterized above all by greatly impeded expiration, whistling and sibilant râles, and acute more or less marked emphysema, the lungs regaining their normal size at the termination of the attack. The peculiar expectoration which will be described further on is also to be regarded as an almost constant phenomenon of the asthmatic attack.

Only to this complexus of symptoms should the designation "asthma" be applied. Frequently, however, not only the laity, but also physicians give the term a much wider application, including under it every possible form of paroxysmal dyspnœa. If the cases of asthma reported in the works of even the more recent authors be submitted to a careful examination, the above-mentioned criteria will often be found wanting; indeed, not infrequently it can be positively determined from the description of the symptoms as well as from the results of the treatment that the cases were not those of genuine asthma. The confusion which still prevails concerning the affection is dependent in no small measure upon this fact.

Asthma and dyspnœa are to be sharply distinguished from each other. In every case of dyspnœa we must first inquire of what kind it is, whether inspiratory, expiratory, or mixed dyspnœa. In contrast with the mixed dyspnœa, the breathing in the first two forms is not quickened, on the contrary, rather diminished in frequency, but that phase of the respiration which is especially impeded is prolonged at the expense of the other. Asthma belongs to that form of dyspnœa in which one respiratory phase, expiration, is especially impeded and prolonged. But always when one phase of the respiration is especially impeded we find that two means of compensation for the impediment are called into play automatically; these are increased power and longer time. Hence we find in asthma that the expiration is accomplished by the aid of the auxiliary expiratory muscles, and that respiration is diminished rather than increased in frequency, but that the expiration is prolonged at the expense of the inspiration.

The second essential symptom is the acute pulmonary emphysema which manifests itself by increase in the dimensions of the lungs and by a peculiar modification of the percussion note, which Biermer called the "box" or "pillow" tone. The mode of production of this acute emphysema, which often develops in a few minutes, is a theoretical question to which we shall return when we consider the theories of asthma. It is certain that this emphysema is absent in no pronounced case of asthma, and that it is directly connected with the attack is proved by its rapid appearance at the beginning, and its

disappearance at the end of the paroxysm. On auscultation the sibilant râles are heard more distinctly in expiration than in inspiration.

As the last important symptom is to be mentioned the sputum, in which the occurrence of Curschmann's spirals and Leyden's asthma crystals is especially noteworthy.

These are the essential symptoms, and only when they are present may we call the affection asthma. Asthma may occur as a primary and idiopathic, or a secondary and symptomatic disease. Primary idiopathic asthma is much more rare than was formerly supposed. It can be said to exist only when the most careful examination can detect no abnormality of any other organ, which can in any way be connected with the occurrence of the attacks. It occurs when the attacks are excited directly by the respiratory centre or by the centrifugal nerves of the respiratory apparatus. Such attacks are certainly rare.

Much more common is the secondary or symptomatic asthma which may also be called reflex. This group includes the large number of cases in which the asthma is caused by pathological changes in othe rorgans. Most frequently it is a morbid state of the respiratory apparatus, of the nose, of the pharynx, of the bronchi, etc., which is the exciting cause of the paroxysm, but affections of quite distant organs may also excite it in a reflex way. That here the attacks are thus reflexly excited is proved by the fact that the disappearance of pathological conditions in the organs in question is followed by a cure of the asthma.

Following Curschmann's example we might divide this secondary asthma again into subordinate groups. Curschmann divides it into cases (*a*) in which the lungs are normal and (*b*) in which they are diseased. But this further classification seems to me of less importance than the first-mentioned division into primary and secondary asthma. If the clinical symptoms show that an asthma is present, it must next be established by means of a minute inquiry into the past history, with a consideration of all the circumstances and by a very careful examination of all the organs, whether the asthma is primary or secondary. Upon the answer to this question depends also the treatment of the case.

This division seems to me the most simple. Many authors distinguish an additional series of sub-varieties. Thus, for example, Brügelmann in his monograph on asthma distinguishes five different groups, a nasal, a pharyngolaryngeal, a bronchial, a neurasthenic, and an intoxication asthma. Such a classification I cannot consider appropriate; it goes too far in some respects and not far enough in others. For this classification has to do not so much with

differences in the form of asthma as with differences in its exciting causes. But reflexes from the most various points may cause asthma. Brügelmann's refusal, for example, to recognize asthma dyspepticum as a separate form because that belongs under neurasthenic asthma, is inconsistent with the rest of his classification, which is based upon the points from which the excitation of the asthmatic attacks proceeds. The name "asthma nasale" means only that the excitation of the asthma comes from the nose; the name "asthma dyspepticum" means only that the excitation comes from the stomach. But, for the disease thus to originate, it is not necessary that the patient should be neurasthenic, and neither the nasal disease nor the dyspepsia in itself constitutes asthma; for that something else is necessary, *i.e.*, an especial predisposition the effect of which is that in one case a disease of the nose, in another a disease of the stomach, in a third psychical emotion causes an asthmatic attack. We do not know upon what this predisposition depends, but we have many analogies for it in pathology. In one case every indisposition causes a migraine, in another a cramp of the stomach, in a third an asthmatic attack. If we wish to put it in different language we may say that the organ affected is the *locus minoris resistentiæ* of the patient. I therefore do not consider it correct to distinguish different forms of asthma according to its various points of excitation. The predisposition to asthma is of chief importance. Even in one and the same patient asthma may proceed from affections of different organs, and the sufferer assigns to-day one thing, to-morrow another as the cause of his asthmatic attack. At one time the cause is a raw east wind, at another mental emotion; again it is the inhalation of certain vapors or the immoderate use of certain articles of food, etc. If we should apply to all these cases the designation "neurasthenic asthma" we should have one more name, it is true, but no increase in clearness, for we do not know upon what this "neurasthenic" tendency to asthmatic attacks depends.

Asthma may be called a nervous disease, a neurosis, inasmuch as it is certain that nervous disturbances play a part in it. But Curschmann is right when he says that the term "nervous asthma" is too general; the name "asthma" is sufficient. The name "spastic asthma" goes too far, for it takes for granted that the condition is one of spasm only, which may be true, but is not yet certainly proved. Even though vasomotor disturbances of the respiratory mucous membrane play a part in the asthmatic paroxysm, as seems to be proved by many facts, yet the name "vasomotor asthma" must be rejected as insufficient. The often used name "bronchial asthma" also carries with it an hypothesis: it assumes that the condition is

one of bronchial spasm. But if the designation "bronchial asthma" is restricted to those cases in which the asthma is connected with a not transient affection of the respiratory apparatus, especially of the the mucous membrane of the finer divisions of the bronchial tubes, it would then be applied to only one limited form of asthma, and that a secondary asthma.

The so-called "asthma cardiale" has absolutely nothing in common with genuine asthma, and the name were better abandoned.

In the following chapters we shall treat only of true asthma as already defined. If for distinction from cardiac asthma a more definite designation is desired, it seems to me better to use the term "asthma pulmonale" instead of the much used but hypothetical term "asthma bronchiale."

Etiology.

As we have seen above, we must distinguish between primary and secondary asthma. In the former the attack would be the direct consequence of an abnormality of the respiratory centre or of its paths of communication; in the latter we must assume that the abnormal excitation of these paths takes place reflexly. If it is correct, as Bergson and Salter supposed, that the essence of asthma is a spasm of the bronchial musculature, the point of attack must be situated either directly in the respiratory centre or in the fibres of the vagus which innervate the bronchial muscles. A definitely established case in which asthma was excited from the centre itself does not exist; the hysterical imitations of asthma of course do not belong here.

On the other hand, many cases have been observed in which it appeared probable that the asthma was caused by swollen tracheobronchial glands. We may explain such cases by the supposition that the varying swelling of the glands produces an irritation of the vagus (Biermer). Williams and Joal believe that a frequent cause of asthma in children is a chronic swelling of the bronchial glands resulting from whooping-cough, measles, chronic bronchitis, or catarrhal pneumonia. These are supposed to give rise to the attack by pressure upon the vagus or its branches.

But much more frequently than through direct excitation of the respiratory centre or of the vagi, asthma is produced reflexly from various peripheral organs. Yet even for these cases we must suppose that an especial predisposition, an abnormally ready excitability of the respiratory centre or of its centrifugal paths is present, the result of which is that an irritation of a peripheral organ, a stimulation of the olfactory nerve, a cold, psychical emotion, or the like excites

reflexly an asthmatic attack. Of course, we do not know upon what this predisposition depends. Doubtless heredity plays a certain part, for not rarely we find asthma inherited through several generations. Thus I once knew a family in which the father and some of the children suffered from asthma, the latter from their earliest youth; the mother was not affected. But the disease immediately disappeared in all the cases, after all possible remedies had been previously employed in vain, as soon as the family left the villa in which they had resided and moved to another. Certainly some of the etiological factors of the disease must have existed in the previously occupied house; but, on the other hand, a special hereditary predisposition must also be assumed, since the whole family was not attacked by asthma. In many cases of hereditary asthma the disease is found to appear in the children at the same age at which it began in the parents, and also to disappear at the same period of life at which it had left the parents. The alternation of asthma with other neuroses which is sometimes observed is interesting. Salter relates a case in which asthmatic and epileptic paroxysms alternated with each other. Eulenburg observed the alternation of asthmatic attacks with hemicrania and with angina pectoris. Not very rarely we find that asthmatics are descended from families in which epilepsy, migraine, neurasthenic affections, and gout prevail. Asthma has often been thought to be especially connected with gout and the name asthma arthriticum has even been given to a special form of the disease.

Men are much more liable to gout than women. All classes of society are not equally attacked. Undoubtedly purely nervous asthma occurs more frequently in the well-to-do and in the middle than in the lower classes. Asthma is not rare even in earliest childhood.

Among the diseases which especially predispose to asthma or through which asthma is most frequently excited, those of the respiratory apparatus are first to be named. To diseases of the nose especially a great and in part an exaggerated importance in the production of asthmatic attacks has recently been assigned. To Voltolini belongs the credit of having first pointed out, in the year 1871, the relatively frequent connection of nasal diseases, especially nasal polypi, with asthma, and of having proved that connection by showing that when the former were cured the asthma disappeared. These observations of Voltolini were soon confirmed by numerous investigators, but were at the same time modified, in that it was found that not only nasal polypi, but also the most various processes in the nose and in the nasopharyngeal space could give rise to asthmatic attacks.

An essentially new theory was advanced by Hack. Since asthma is observed in only a small proportion of the cases of nasal polypi, while in the majority of cases all nervous accompaniments are absent, he concluded that the polypi in themselves did not cause the excitation, but that besides this affection another factor must be present. This factor he believed to be present in the mucous membrane over the turbinated bones of the nose, these turbinated bodies forming a connecting link between two reflex processes. On the one hand reflex processes which may have their origin in an especially irritable condition of the nasal mucous membrane itself produce a turgescence of these cavernous spaces; on the other hand reflexes which often manifest themselves in remote regions, asthma, migraine and others, arise from the swollen organs.

The view of Hack that reflexes are produced only through the agency of this erectile tissue has, however, been proved to be too narrow. It has been proved by numerous observers that reflexes may arise from every point in the nose and without the agency of the erectile tissue. Nevertheless, as Schech especially insists, the turbinated bodies may play a part in certain forms of asthma. Schech classes under this head a part of those asthmatic cases with nasal affections in which the attacks occur only during sleep. In these cases the asthmatic attack is excited not only by contact but also by changes in the mechanism and the chemistry of respiration. The mechanism of respiration is changed in that, by the swelling of the erectile tissue of the nose, respiration through the nose becomes impossible and the sleeper is suddenly forced to breathe through the mouth, and so is at once subjected to all the disadvantages of mouth breathing, the inhalation of colder, dryer, and unpurified air. This sudden change in the mode of respiration and in the inspired air in sleep may cause asthma in cases of general or local hyperæsthesia of the nervous system, as those numerous asthmatics show who at once lose their asthma on simply changing their place of abode. But the chemistry of respiration is also changed in consequence of partial or complete stoppage of the nose during sleep. The blood becomes deficient in oxygen and thus the innervation of the brain is affected.

However this may be, it is certain that nasal diseases of every kind and asthma are very frequently found together, and that by a suitable treatment of the nasal affection the asthma may be cured. Another question is this, whether, and how frequently, the cure is permanent. In most cases this question cannot be decided for lack of a sufficiently long period of observation. That the improvement is often enough only temporary every one has learned who has observed a considerable number of such cases for a long time. This

should hardly excite surprise, for the disease of the nose *per se* is not necessarily followed by asthma. The asthmatic attack is indeed excited by it, but for such excitation an additional factor is also necessary, *i.e.*, a special irritability of the respiratory nervous apparatus. But this latter is not changed by the local treatment of the nose—one peripheral point of attack only is removed. It is therefore not strange if, after a time, in spite of the cure of the nasal affection, the asthmatic attacks recur; for the predisposition still persists as before and only a single point of excitation has been removed. But patients are often seen in whom asthma is excited not only from the nose but also from other parts of the respiratory apparatus, and even from other organs. Now the attacks are confined to the time of menstruation, again psychical emotions or other influences, colds and the like, excite such an attack. Nevertheless, even in such cases, if the nose causes the patient annoyance or if the objective examination detects any morbid change in it, local treatment is certainly in place.

According to Hack's theory, reflexes are excited only through the erectile tissue; accordingly the elimination, that is to say, the destruction of the erectile tissue, should remove the asthma. This assumption has not been proven to be correct. When any abnormality of the nose is present which can be connected with the asthma, this should be removed. But we must not overlook the fact that in so doing we remove only a single source of stimulation of the attacks, not the predisposition to the attacks itself.

To that form of asthma which is caused by nasal affections is most closely allied the so-called hay fever or hay asthma which in some countries, especially England and America, is a frequent, but with us a rare form of disease. Many have thought that hay asthma should be regarded as a special type, particularly on account of the phenomena connected with the circulatory system which manifest themselves in the form of more or less well-marked hyperæmia of the mucous membrane of the air passage, increased secretion of the nasal and bronchial mucous membrane, increased lachrymal secretion, sometimes even very transient œdema of the face and urticaria. On account of these phenomena it has even been thought that hay asthma should be regarded as the typical vasodilator form in the Weber-Störk sense of the term. I cannot accept this view. The above-mentioned phenomena by no means constitute hay asthma. We can only use that term when the already described manifestations of asthma, the typical attacks with expiratory dyspnœa, acute pulmonary emphysema, sibilant rhonchi, etc., are present, not when catarrhal symptoms, coryza, conjunctivitis, bronchitis, supraorbital

neuralgia, etc., alone occur. The proper terms for the latter series of symptoms are hay fever, hay cold, and the like. The catarrhal and vasodilator phenomena may be present without asthmatic attacks resulting.

The exciting cause is well known to be the pollen of certain grasses, not, as was formerly supposed, the pollen of a single kind of grass, but of various grasses. In England the Anthoxanthum odoratum, in Germany the rye blossom, in America the Ambrosia artemisiæfolia are regarded as especially responsible for the disease.

Without doubt hay asthma is a nasal form of asthma in that the attack is excited from the nose. But these attacks appear only when a predisposition to asthma is present. Cure of hay asthma from local treatment of the nose has often been observed, but that in hay asthma only a peculiar exciting cause, not a special form of asthma is present, is shown by the fact that the affection can perpetuate itself not simply as an asthma appearing at the time of the hay harvest but as ordinary asthma. Thus Sée has related a case in which a sufferer from hay asthma, after the disease had recurred for twenty summers, finally acquired a lasting dilatation of the right heart. Of this patient's three daughters, two suffered from typical asthma. But cases are not rare in which the patients suffer not only from hay-asthma but also from other asthmatic attacks.

Hay fever, hay coryza, and hay asthma are then to be sharply differentiated. We should use the term hay asthma only when the entire complexus of symptoms of the asthmatic attack is present, not when there are merely catarrhal symptoms, such as coryza and the like.

Like the pollen of certain plants, other irritants of the nose may excite asthma in the predisposed. Asthma caused by ipecacuanha has been repeatedly observed. Cullen tells of an apothecary's wife who had an attack of asthma whenever ipecacuanha was triturated in the shop. Trousseau relates with regard to himself that he always had an attack of asthma if he remained in a room in which there was a bouquet of violets. Itzigson reports the case of a merchant who always had an asthmatic attack if fresh coffee was handled in his presence, and another speaks of a dyer who had asthma when working with the wood of Quercus tinctoria.

To these forms, since they are produced by abnormal sensitiveness to certain odors, the name "asthma idiosyncraticum" has been given, a term which is not particularly apt. Idiosyncrasies play a part in many forms of asthma as well as in hay asthma. But that in these forms the psychical factor may be of importance is shown for example by a case reported by Mackenzie. It was that of a lady who always had an attack if she smelled a rose. One day Mackenzie

held an artificial rose before her, when an attack occurred as before. In this case the idea of the irritation which at other times caused the attacks was sufficient to produce one. But this case also shows that in an individual who is predisposed to asthma and in whom the point of excitation is peripheral, here for example the nose, the attack may be excited in a purely psychical way without irritation of the peripheral organ.

How difficult it sometimes is to find the exciting cause of the attack is shown by a case recently reported by Dünger. The patient, who was thirty-two years of age, had begun to suffer from asthma in his fifteenth year. In the following years the signs of tuberculosis of the lungs became increasingly prominent, and at the same time the trouble from asthma increased. Residence in Davos brought improvement to the tuberculosis, and an operation on the nose caused an almost complete disappearance of the asthmatic attacks. After six months the asthma returned. Sometimes the patient noticed that upon a change of locality or even of the bed there was a sudden return of the attacks, at other times that the attacks which had been violent ceased as suddenly. In latter years the attacks had stopped almost entirely, but recurred again in this year. The patient removed to another town. At once the asthma, which had been almost entirely absent for four years, returned. One day the patient made the following discovery: In the night he had a violent attack, he got up and lay upon a sofa in the adjoining room. The attack ceased immediately. This experiment had always the same result. Hence he began to suspect that the mattress, the peculiar odor of which attracted his attention, was to blame for the asthma. He changed the mattress, and from that moment the asthmatic attacks disappeared.

As from the nose, an asthmatic attack may also be excited from the pharynx, the larynx, or the bronchi. To certain diseases of the bronchi an especial importance in the causation of asthma has recently been assigned. As is well known, Laennec and Brée supposed that diseases of the bronchi were directly connected with asthma, but their views attracted no further attention under the influence of the ever more widely accepted theories as to the purely nervous nature of asthma, until Leyden in his well-known work "Zur Kenntniss des Bronchialasthma" again directed attention to the changes of the bronchial mucous membrane in this disease. In the year 1871 he first pointed out the fact that in asthma a peculiar secretion is formed in the bronchial tubes. In this expectoration he found numerous threads and plugs in which the crystals already discovered by Charcot in other diseases were detected. Leyden assumed that from

time to time a peculiar lymph-like mass was poured out into the alveoli of the bronchioles, that this mass remained there until it had become inspissated, and crystals had formed, and that thus bronchial spasm was secondarily produced.

We are indebted to Curschmann for especially thorough and careful investigations as to the nature of the sputum in asthma. Curschmann's work culminated in the demonstration that there is a peculiar chronic disease of the bronchioles which is with especial frequency combined with asthma. This is characterized according to him by a peculiar viscid sputum, like the white of an egg, in which, according to the nature of the individual case and the time of the examination, a greater or lesser number of very characteristic formations are to be found, the spirals and central threads, and, closely connected with these, the crystals described by Leyden. Curschmann believed that this form of disease should be sharply separated from the common catarrhal affection of the bronchioles as well as from fibrinous bronchiolitis, and proposed for it the name, which is now pretty generally accepted, of exudative bronchiolitis. This he regarded as a completely independent disease, but a disease which very frequently, or when the malady has reached a certain development nearly constantly, leads to asthma. Therefore, according to Curschmann, for the production of asthma the mere existence of a bronchiolitis does not suffice, but there must be a certain extension of the disease through the bronchi and a certain irritability. The duration of the process is also of importance, since only the chronic form leads to asthma, the acute exudative bronchiolitis running its course without causing asthmatic attacks. Hence the bronchiolitis plays only the part of a predisposing factor which reflexly excites the asthmatic attack, in a way analogous to that of the diseases of the nose previously mentioned.

But here it should be stated that this conception has not been accepted without dispute. Of the fact of the frequent, indeed almost regular, occurrence of spirals and crystals there can be no doubt, but it is another question whether these spirals are the cause or the products, the accompaniments or the results of the asthma. Another question is whether the change of the mucous membrane in question and the diminished permeability of the bronchi through its products do not alone suffice to explain the complexus of symptoms of asthma without recourse to a spasmodic element. This view has also been defended especially by Ungar, who has attempted to explain the symptoms of the attack in a purely mechanical way, by the fact of obstruction. But the opinion has been expressed by Schech, B. Fraenkel, and others that Curschmann's spirals are not the cause but

only a consequence, a secondary product. In support of this view special weight has been placed upon the fact that spirals and crystals are also found in cases of nasal asthma, and that in cases where the attempt to cure the asthma by treating the nose was successful, the sputum and the spirals disappeared. But we cannot enter further into the discussion of this question here, since we are concerned only with the relation of bronchiolitis to asthma. We shall return later to the question whether it is the cause, the consequence, or the accompaniment of asthma.

It would lead us too far to enumerate singly all the other organs which have been brought into etiological connection with asthma and from which an attack may be excited reflexly. We need only mention asthma vernale, uterinum, verminosum, dyspepticum, and the like. But these terms have been much misused. Any one who attentively examines the literature of these forms of asthma will certainly admit that by far the greater number of the cases described as asthma dyspepticum, uterinum, etc., are not genuine cases of asthma. The same can be said of a series of cases which have been described as psychical asthma. I have already cited an observation which proves that the mind plays an important part in the etiology of asthma. But cases have often been described as psychical asthma which have nothing to do with genuine asthma. Thus Hecker very properly calls attention to the fact that a state of anxiety in neurasthenics is sometimes confounded with asthma. Patients were repeatedly sent to him with the diagnosis of asthma in whom a single observation of the attacks sufficed to establish the fact that they were not asthma at all, but typical attacks of anxiety.

That asthmatic attacks may be caused in the predisposed by psychical excitement is well known. For these cases in which the characteristic phenomena of asthma are present the term "psychical asthma" may be reserved, but it should not be applied to cases of anxiety connected with dyspnœa like those mentioned above. The name "asthma," as I cannot too strongly insist, should be reserved for cases in which the already described complexus of symptoms is present, viz., expiratory dyspnœa, acute pulmonary emphysema, sibilant râles, and the like.

Of other predisposing causes climatic conditions should first be mentioned. Asthma occurs undoubtedly with greater frequency in some regions than in others. It seems to be especially frequent in England and North America. The fact which has been especially emphasized by Trousseau, that certain patients are attacked by asthma in some localities and not in others, is important. Every one who has seen many asthmatics can report such observations.

A general law with regard to the influence of the seasons cannot be formulated. Some asthmatics feel better in summer, others in winter. Sudden changes of the weather and wind are unfavorable. Rosenstein has stated that in Gröningen the northeast wind is especially unfavorable, and that patients there predict attacks when it begins to blow.

Night is to be mentioned as one of the best-known predisposing causes. Many patients have attacks only in the hours of darkness. In many of these cases the attacks do not occur if a light is left burning. In many patients the attacks occur regularly at the same hour, in others irregularly. Thus Trousseau, who himself suffered from asthma, relates that his attacks occurred regularly at three o'clock in the morning.

Among other predisposing factors the relations of chronic skin diseases to asthma deserve notice. Döllinger maintained that asthma, which is said to be met with more frequently in warm than in cold countries, was often caused by the "driving-in" of herpes, and that it appeared very frequently after the disappearance of herpetic affections. Patients whose asthma dates from early youth often state that they had suffered in childhood from obstinate skin eruptions. In other cases we see asthma combined with psoriasis, eczema, and other affections of the skin. Waldenburg called attention to the fact that sometimes a certain reciprocal activity is observed between eczema and asthma, in that one disappears or diminishes when there is an exacerbation of the other. Blanchez reported to the Société Médicale des Hôpitaux in 1883 a case of a child of twelve years who had suffered from eczema since his second year and in whom the remission of this eruption was always succeeded by violent attacks of asthma.

The congenital enlargement of the thyroid gland has been believed to be a not very rare cause of asthma in children. Through this the entrance into the laryngeal cavity is narrowed, and thus asthma is supposed to be induced. This view shows again how loosely the term asthma has been applied. That a mechanical narrowing of the lumen of the larynx can cause dyspnœa is a matter of course, but this dyspnœa, aside from the fact that it is more or less continuous, is never expiratory and has no relation in any way with asthma.

Lead has also been brought into connection with asthma and an especial form, "asthma saturninum," has been distinguished. Although I have observed many cases of lead poisoning of widely differing degrees of severity, I have never seen typical asthmatic attacks which could be regarded with certainty as the result of such poisoning. The assumption is the more natural that if under the

influence of lead dyspnœic attacks develop, they are to be referred rather to abnormalities of the heart's action than to spastic states of the bronchi or diaphragm.

These are the most important actual and alleged exciting causes of asthma, although in the foregoing enumeration all the possibilities are of course not exhausted. But most important of all is always the predisposition, the peculiar change in the irritability of the respiratory nervous apparatus, the result of which is that trivial irritations of the most different kinds and from the most different sources produce the spasmodic attack.

Symptomatology and Course.

Asthma is a paroxysmal disease characterized by attacks of more or less highly developed dyspnœa which recur generally at irregular, more rarely at regular intervals. In the intervals the patients feel well, provided that there are no complications or that no sequelæ have developed, such as are found after a considerable duration of the disease. The attacks occur more frequently in the night than in the day, and they generally begin suddenly and unexpectedly. The patient, who has enjoyed a good and quiet sleep in the first hours of the night, awakes suddenly with a feeling of oppression and anxiety, which rapidly increases and becomes severe. Respiration becomes increasingly more difficult. The breathing, especially the expiration, is sighing and whistling. It is impossible for the patient to remain in bed even in a sitting posture. He springs out of bed and supports himself, generally bending forward upon a chair or table. His brow is covered with cold sweat, his hands are cold and damp, and his face becomes more and more cyanotic. The patients often assume the most singular positions to satisfy their hunger for air, most frequently they prefer to bend forward. The appearance of the patient shows that his breathing is labored and difficult; his loud whistling respiration is heard at some distance. But the breathing is not at all quickened, on the contrary it is slower than normal and the plainly audible expiration is especially prolonged. In spite of all his efforts, in spite of the assistance of numerous accessory muscles of respiration, the patient does not succeed in satisfying his hunger for air. This condition continues unchanged for a varying time, sometimes, in rudimentary attacks, for only a few minutes, but in typically developed attacks, for one, two, or three hours, or even much longer. Generally, unless influenced by treatment, the dyspnœa diminishes gradually, the extremities become warmer again, the cyanosis becomes less, the loud sighing and whistling give place to a moist rattling, so that the patient can now expec-

torate, and thus all the symptoms of the attack gradually disappear. More rarely it happens that the attack, left to itself, suddenly ceases, and the patient states that he has the sensation of a sudden relaxation of the spasm. After such a violent attack the patient usually feels much exhausted, and he now falls into a deep, quiet sleep from which he awakes with completely free respiration, although he is still somewhat fatigued.

Such is the picture of the typical asthmatic attack, which recurs at now longer, now shorter intervals, in some cases almost daily, in others after long and irregular intervals.

But there are numerous variations from this typical picture of the disease, and there may even be quite rudimentary attacks in which the essential features of asthma are only barely indicated, and the fact that in such cases typical and severe attacks alternate with the rudimentary attacks alone makes it possible to estimate correctly the significance of the latter.

But while, as a rule, asthma occurs quite suddenly and unexpectedly in perfect health and without a demonstrable cause, in certain cases we see that prodromes, quite similar often to the aura epileptica, precede the outbreak a longer or shorter time, by which the patient is apprised of the approach of the attack. Sometimes the attack is preceded by violent sneezing, by an acute coryza with abundant nasal secretion, sometimes by a tickling in the larynx which causes cough, sometimes an abnormal sensation at the pit of the stomach, or yawning which the patient is unable to suppress indicates that a paroxysm is impending.

In many other ways also variations occur from the picture already given. While as a rule only one attack takes place, which is succeeded by a long and completely free interval, in some cases a series of attacks occurs. The attacks continue a number of days with only slight intervals before they give place to a longer and complete remission.

Numerous variations also occur with respect to the time of the attacks. It is a noticeable fact that in many patients the attacks always occur at the same hour. Thus Trousseau relates, with regard to himself, that for a considerable time he always had his attacks at three o'clock in the morning, while his mother's attacks took place between eight and ten o'clock in the morning. He also speaks of a tailor who was so regularly attacked with asthma, at three o'clock in the afternoon, that it suggested a masked intermittent fever.

In children also, in whom asthma is by no means so rare as is often supposed, many deviations from the typical form are found.

As was pointed out by Trousseau, the catarrhal form is more frequent in them, since the phenomena of bronchitis are especially prominent, while the diagnosis is made easy by the fact that the degree of the dyspnœa bears no relation to the findings of auscultation. It is quite possible to confound this form of asthma with a simple bronchial catarrh; but, on the one hand, the lack of correspondence between the well-marked nervous phenomena and the trivial catarrhal changes, and on the other the absence of fever, the efficacy of antispasmodic remedies, as well as finally the rapid disappearance and the just as sudden and apparently causeless return of the attacks, should make it possible to establish a correct diagnosis.

In discussing the individual symptoms whether prodromes have preceded or not, the most striking symptom is the marked dyspnœa which increases rapidly to the highest degree. The patient seeks in every way to satisfy his hunger for air. He rushes from his bed, opens the window, and bends forward, supporting himself by his arms in order to effect expiration more readily by the aid of the firmly contracted abdominal muscles. The patients are almost never able to remain in bed. As a rare exception and not at all corresponding with the behavior in common asthma, must the case of Bamberger's be regarded, in which the patient during the attack always lay upon his back, never attempted to sit up, and made no movement except that, when the spasm had become very violent, he moved his body restlessly from side to side. Of course asthmatics with a high degree of dyspnœa avoid all extensive movements, but the maintenance of a horizontal position does not belong at all to the picture of asthma. Sometimes the patients sit upright in bed supporting the arms firmly, sometimes they hurry to the window, again they take refuge in an armchair.

The respiration is extremely labored and noisy. During both inspiration and expiration, loud whistling sounds are heard even at a distance, more loud and intense in expiration which is considerably prolonged and is performed by the aid of all the available expiratory forces. In the face, which is cyanotic, are depicted the extreme hunger for air and the despair of the patient. The respiration is dyspnœal to a high degree, but the number of respirations is not increased, on the contrary, usually diminished. The relative length of the inspiration and expiration is altered. Inspiration is proportionately short, but deep and strong. The upper part of the thorax is strongly elevated while the lower part is but little or not at all enlarged. The change of form of the thorax is chiefly an increase upwards. At the same time the sternomastoids, the scaleni, and other muscles are strongly contracted. Expiration presents deviations from the normal

to a much greater degree than inspiration. In contrast with inspiration, which, as Bamberger well says, does not differ from an ordinary powerful and somewhat forced inspiration, expiration is characterized by the most strenuous effort. All the accessory muscles of expiration are spasmodically contracted and the abdominal muscles are tense and hard, in consequence of which even involuntary passage of urine and fæces may result. But in spite of all his exertions the patient does not succeed in essentially diminishing the size of his thorax.

With reference to the state of the trachea it should be mentioned that Stoerk observed a considerable reddening of the mucous membrane of the trachea and the bronchi.

Percussion during the attack often shows a considerable increase downwards of the border of the lungs, diminution of the heart dulness, and a low position of the liver, while the respiratory movement of the edges of the lungs is much diminished. At the same time the character of the percussion note is changed. It becomes hypersonorous, a modification for which Biermer has proposed the name "box" or "pillow" tone—for every horsehair pillow gives this note. This change of percussion note, which is the consequence of the acute emphysema, disappears at the cessation of the attack and the return of the expanded lung to its normal dimensions.

In auscultation the first thing that attracts attention is that the vesicular respiratory murmur is heard in some parts of the lung but feebly; in others, especially the lower parts, not at all. On the other hand, corresponding to the whistling, which is audible even at a distance, sibilant râles, denoting the stenotic inspiration and expiration in the smaller air tubes, are heard especially during expiration. Towards the end of the attack moist râles appear in the place of these, and at the same time expectoration becomes established. At the beginning and during the height of the attack cough is generally not present or is unimportant. It becomes prominent only towards the end of the attack when the râles have become moist. It is evident that under the given circumstances during the attack coughing as well as speaking must be in a high degree burdensome and difficult.

Fever is not a feature of asthma. If it is exceptionally observed in the asthmatic attack, its origin is due not to the asthma *per se*, but to complications. On the contrary, a surprisingly low bodily temperature is not rarely observed during the attack, and the peripheral parts of the body especially are not only distinctly cyanosed, but also remarkably cool. It is true that sometimes a febrile asthma is met with in children, but in them, as has already been mentioned, asthma occurs especially in the catarrhal form, and catarrh alone in

children is sufficient occasionally to cause a slight febrile movement; the superadded asthma, the tendency to spasm, or whatever may constitute the essence of asthma, has nothing to do with the fever.

The heart's action is, as a rule, quickened during the attack; at the same time the pulse is generally smaller and weaker. But this acceleration of the pulse is usually not very marked. It never reaches so high a degree as in neuroses of the vagus. Many of these cases, as I first pointed out, besides an extreme acceleration of the pulse present a certain similarity to the asthmatic attack, in that here also an often considerable emphysema of the lungs develops acutely. But they are easily distinguished from genuine asthma by the quickened respiration, the extreme acceleration of the pulse, the absence of sibi-

Fig. 1.—Curschmann's Spirals, Natural Size.

lant râles, etc. More rarely the pulse in asthma is of normal or even subnormal frequency.

The character of the sputum in asthma is of especial interest and of great diagnostic importance. Most asthmatics expectorate not at all or but sparingly at the beginning and during the height of the attack. Towards the end of the attack there is a somewhat more abundant expectoration of a generally viscid, frothy mucous sputum; this expectoration, as a rule, continues for a time after the attack has ceased. Leyden has the credit of having first called attention to the especial peculiarities of the sputum of asthma. This sputum is of a grayish-white color, extremely viscid, and sometimes quite frothy. Its amount varies, being sometimes scanty, sometimes abundant,

amounting to one hundred or even several hundred cubic centimetres. In this there are found many small whitish-yellow or yellow flakes, threads, and plugs in a transparent, almost glassy, medium. Microscopically, as Leyden first demonstrated, these bodies consist of closely aggregated roundish cells in the midst of which Leyden's asthma crystals are found in a greater or less number. Besides these, cells of cylindrical ciliated epithelium from the bronchi are often met with. The structures known under the name of Curschmann's spirals are also found in these plugs, especially in those of a grayish-white color. These vary in form and size. In many (Fig. 1)

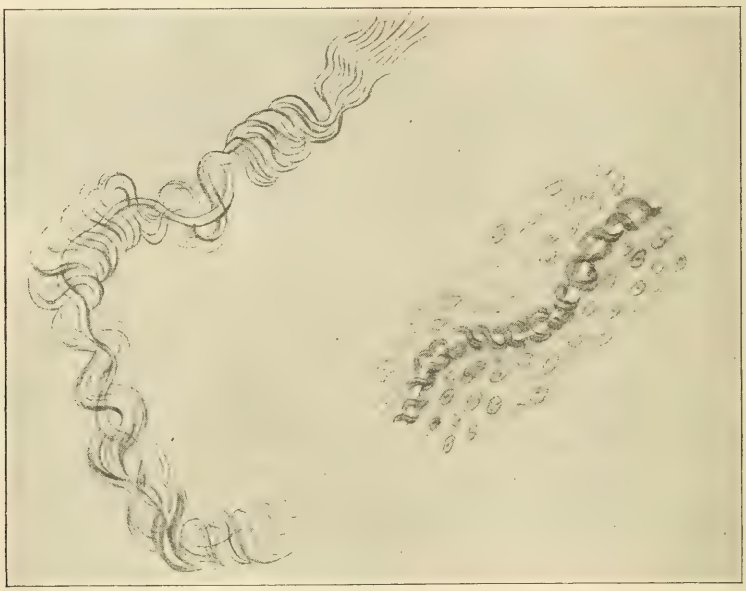

Fig. 2.—Spirals Wound Round a Central Thread (after Curschmann).

the spiral structure, in some (Fig. 2) even the longitudinal whitish streak can be recognized macroscopically. These thread-shaped formations are of a very firm consistence, and can hardly be crushed under the cover-glass. The spirals are abundantly covered with round and spindle cells and alveolar epithelium, also here and there with single ciliated cells. The spirals are often recognizable by the naked eye or by means of a magnifying glass; at other times they can be detected only by microscopical examination. In many of these spirals there is seen a bright shining sometimes much tangled band of varying width, about which threads are wound spirally (Fig. 2). This central band or thread is, as a rule, very thin, is shining

and extends through the axis of the spiral. It is sometimes found isolated, surrounded only by a mass of mucus. It is colored intensely by aniline dyes. The spirals vary greatly in form; sometimes they are arranged regularly about the central thread, sometimes they occur irregularly and singly.

In order to determine the intimate nature of Curschmann's spirals, Schmidt has studied hardened and stained sections of the sputum. Weigert's method of staining fibrin proved to be the best for the demonstration of the spirals in the sections. As for the chemical constitution of these formations, since Schmidt's investigations, there can be no doubt that the central threads of the spirals, at least the typical forms described by Curschmann, consist of mucin, not fibrin. There has never been any doubt as to the mucous nature of the spiral threads. With respect to composition, there is therefore no difference between the central threads and the spirals. Both consist of mucus. The central thread, as Ruge has shown, consists simply of a thickened and twisted thread of mucus.

Here it should be mentioned that spirals occur not only in asthma, but also occasionally in other diseases of the respiratory tract. Thus they have been found, though rarely, in the sputum of pneumonia, of fibrinous bronchitis, and of acute and chronic catarrhal capillary bronchitis. That is, they appear to occur only in such diseases as affect the smaller bronchi and the bronchioles.

Opinions differ as to the mode of formation of the spirals. Curschmann, their discoverer, supposes that the central threads are formed in the finest bronchioles and receive their spiral form in their passage into the larger bronchioles by being squeezed out, as it were, through the mouths of the finest bronchioles, whereby he assumes that there is a spirally shaped opening of the smaller into the larger bronchioles. On the other hand, Pel thinks that the chief factor is the passage of a viscid elastic mass through a very narrow canal (the bronchioles) under the influence of the ciliated cells and the irregular contraction of the muscles of the bronchi and of the diaphragm. Lewy regards the central thread as a product of the secretion of the mucous cells.

Schmidt had an opportunity of studying the mode of formation of the spirals in a case of asthma in which death occurred during the attack. In both upper lobes nearly all the bronchi of a diameter of from 1 to 3 mm. were completely filled with a tough glassy mucus, while in the lower lobes the majority of the bronchi were free. This mucus adhered very firmly to the walls; when pulled out from the lumen the whole mass seemed twisted. Typical Curschmann's spirals with central threads were demon-

strated microscopially in these masses of mucus. On microscopical examination of the hardened lung it appeared that most of the smaller bronchi, the epithelium of which was well preserved, were dilated and filled with a homogeneous mass consisting mainly of mucus. In these masses there were found the most various sections of spirals. In the larger bronchi of the second order every possible form of transition from the typical spirals was present, but those from the bronchi of the first order were less perfect. It could be demonstrated that the actively secreting glandular cells differed in no way from those of other mucous membranes, and that the contents of their ducts showed nowhere a peculiar consistence or twisting. Moreover, typical central threads were present even in the smaller glandless bronchi. Schmidt believes therefore that the view that the central threads are a product of secretion of the mucous glands is not tenable. With respect to the mode of formation of the spirals, it must be regarded as probable theoretically that the force which causes this twisting is not confined to one distinct spot, but is active throughout the entire passage of the bronchial contents as far as to the larger bronchi. Schmidt supposes that it is the rotary motion of the expired air which forces its way through and twists the viscid masses of mucus in the bronchi.

It is clear that the fundamental condition for the production of the spiral twisting is the viscidity of the sputum. In my opinion Hofmann is right when he supposes that the terminal twigs of the entire bronchial tree end in spirals. At every inspiration the bronchi must follow the inspiratory enlargement of the lungs. As Hofmann was able to demonstrate by a metal cast, the larger branches of the bronchial tree pursue this corkscrew-like course, and we may well assume that it is continued into the finest ramifications. But if a viscid mass is pressed through a fine tube of such a shape it must become spirally twisted. Hofmann therefore believes that the formation of spirals is to be explained on the one hand by the anatomical structure, on the other by the viscidity of the mucus.

A peculiar form is that of spirals which contain air (Fig. 3). They were also depicted by Curshmann, and are found with the others.

The much-discussed question as to the occurrence of fibrinous coagula in the sputum of asthma has hardly been capable of receiving a positive answer by means of the methods of investigation hitherto employed. But by means of Weigert's method and the use of the tri-acid stain Schmidt succeeded in demonstrating more or less numerous coagula of fibrin in the sputum of six out of eight cases of asthma. But these coagula were always clearly disinguishable from

the spirals which were also present. As Curschmann claimed, the fibrinous casts have manifestly nothing in common with the spirals.

Eosinophile cells are found in the sputum of asthma, as well as in the fibrinous coagula, and Schmidt has also demonstrated the presence of granular cells (*Mastzellen*) in small numbers.

With respect to the origin of Leyden's crystals, it must be supposed that a substance is present in the sputum which can pass into this crystalline state. The theory was first announced by Gollasch that Leyden's crystals are crystalline derivatives of the eosinophile cells. Seifert's investigations support this view. On histological

FIG. 3.—Air-Containing Spirals. (After Curschmann.)

examination of portions of the nasal tissues from which, after some hours in the moist chamber, numerous crystals were formed, great numbers of eosinophile cells were found; while conversely, in portions of tissues in which no crystals were formed in the moist chamber, only a few eosinophile cells were present.

The number of Leyden's crystals in the sputum of asthmatic patients varies greatly; on some days they may be entirely absent. The investigations of Seifert have shown that the crystals occur most abundantly in the sputum when the expectoration during the presence of an asthmatic catarrh becomes much diminished. It was further shown that in sputum with large numbers of eosinophile cells but

no crystals, just as in mucous polypi after standing for some hours in the moist chamber, Leyden's crystals formed after an interval varying from a few hours to one and a half days. Repeated examinations of such sputum revealed hardly a single well-preserved cell with eosinophile granules, but showed large numbers of the granules lying free.

As is well known, the Charcot-Leyden crystals have often been regarded as identical with Böttcher's spermatic crystals. As Cohn has shown, this is incorrect. With trifling variations the Charcot-Leyden crystals always have the same form. Their chief form is that of a long double pyramid with straight edges and sharp corners. Böttcher's crystals present only a superficial physical resemblance to

FIG. 4.—Leyden-Charcot Crystals. × 800. (After Leyden.)

them; from a crystallographical point of view they are quite distinct. Leyden's crystals (Fig. 4), which are identical with Charcot's crystals from leukæmic blood, are completely colorless, easily crushed, and of widely varying size, in general appearing to be larger when the attack of asthma has been of long duration. They are easily recognizable only with a high power, preferably an immersion lens. If the sputum of asthma is kept in a moist chamber it is often possible to see a remarkable increase in size of the crystals.

In the sputum these crystals are chiefly found in yellow or greenish-yellow threads and flakes. These yellowish flakes and plugs are distinguished from the common purulent constituents of the sputum in that they are not symmetrically round but have a very irregular

surface and an extremely tough consistence, so that it is often difficult to spread them out under the cover-glass. Their appearance under the microscope is that already described by Leyden. Closely packed roundish cells, of the size of a large mucous corpuscle, are seen filled with numerous dark granules; similar granules lie free among these cells, and in the midst of this accumulation of round cells are the crystals.

While on the one hand spirals without crystals, and on the other aggregations of crystals without spirals are met with, cases also occur in which the spirals themselves are covered with crystals. Such flakes have a yellowish appearance, those which contain only spirals being gray. The same aggregations of round cells which Leyden described as containing the crystals are seen to surround and cover the spirals.

As for the significance of Leyden's crystals, an important rôle must be ascribed to them in view of their almost constant occurrence in asthma. Single negative results in the search for them are of the less weight because there are very minute forms which might easily be overlooked, and because they are not always present in abundance during all parts of the attack. Another question, and one that is still open, is what their rôle is, whether, as Leyden thought, they excite the spasm of the bronchial muscles, or whether they are secondary products. We shall return to this question when considering the theories of asthma. Whatever part they may play, it is certain that they are directly and closely related to asthma.

Besides these crystals, Lewy also occasionally found crystals and amorphous masses of phosphate of lime in the sputum of asthma. These are of no especial importance, but may perhaps give rise to confusion, since the thin spindle-shaped needles in which calcium phosphate sometimes is found are quite similar in appearance to Leyden's crystals. Von Noorden also found in the sputum of asthma, cells containing yellow and brown masses of pigment. The addition of hydrochloric acid and ferrocyanide of potassium produced a blue color, showing that the cells contained iron (hæmosiderin cells). Examination of these cells showed that a part, almost half of them, were leucocytes; a small number of cells contained eosinophile granules, but the great majority of the abundant eosinophile cells were devoid of pigment; about one-half of the cells were recognized to be epithelium. These pigment cells were, for the most part, crowded together in masses in the sputum. As for the origin of the pigment, it is well known that not very rarely minute traces of blood are present in the sputum of asthma. Such hemorrhages von Noorden regards, I think correctly, as the source of the hæmosiderin pigment,

in which case it is apparent why the hæmosiderin cells are sometimes present and sometimes absent.

There is little to be said concerning the other symptoms of the asthmatic attack. The general health is as a rule much disturbed at the time of the attack. The patient feels extremely weak. The consciousness is usually in no way affected, but rarely the patient appears somewhat stupid. Quite exceptionally indications of opisthotonus and tetanic spasms are observed, such cases reminding us of the already mentioned relations between asthma and other nervous affections like epilepsy.

Headaches and other neuralgic pains, especially in the distribution of the supraorbital nerve, may occur at the same time as asthma. They are most frequently observed in the nasal forms of the disease, especially in hay asthma. Here neuralgias and asthmatic attacks sometimes alternate.

The urine presents no characteristic peculiarities. Sometimes in very severe attacks there is strangury or even the involuntary passage of urine. The urine is generally concentrated during the attack and frequently deposits a sediment of chlorides.

After the attack the patient feels wearied and exhausted, but soon regains his usual health. This is true, of course, only of cases in which the attacks are separated by a considerable interval and in which complications and sequelæ are not present.

There are the greatest variations in the frequency of the attacks. In some cases for a long time they return only after great intervals, in others they are from the beginning very violent and frequent, in still others they recur quite regularly. Sometimes they increase suddenly in frequency without any demonstrable cause, sometimes they disappear suddenly for a long time without any apparent reason.

The health of the patient between the attacks depends of course upon the presence or absence of complications or sequelæ of the asthma. They often suffer in the intervals with bronchitic symptoms. After long duration of the disease the acute pulmonary distention, which always recurs during the attacks, passes into genuine emphysema, and the elasticity of the lungs suffers. In this stage the patient is not completely free from suffering even in the intervals. He suffers constantly from shortness of breath, at least on active exertion, also from frequent cough.

On the other hand, there are also cases in which the asthma supervenes secondarily upon a bronchitis of long standing with or without simultaneous emphysema. Under these circumstances it is not strange that the patients do not feel entirely well between the attacks, and that they suffer constantly from a generally slight shortness of

breath. With regard to the heart, it is the rule that it remains intact in genuine asthma. Only when the asthma has lasted for years and when secondary emphysema and chronic bronchitis have developed, do we find signs of heart weakness, cyanosis, dilatation of the right heart, and finally cardiac insufficiency and even dropsy. In this stage the attacks, as a rule, almost or quite disappear.

The digestive organs in purely nervous asthma are not particularly affected. Although a few authors state that constipation and a tendency to flatulence are present in the asthmatic patient, yet these symptoms can hardly be brought into direct connection with the asthma. It appears to be a purely arbitrary hypothesis to explain this tendency to constipation by the deficient energy of the expiratory muscles. Since the expiratory muscles are called more strongly into play by the attacks, we should expect, on the contrary, that they would act more efficiently. That constipation is sometimes met with in asthma is not strange, but it cannot be regarded as of especially frequent occurrence. The assertion that dilatation of the stomach is a consequence of asthma seems even more unreasonable. Among thousands of cases of gastric dilatation I have not seen a single one in which that disease could be connected with asthma.

With regard to the blood, it should be remarked that an increase of the eosinophile cells has been found in the blood of asthma patients by various authors (Müller, Gabritschewsky, von Noorden, and others). In five cases of asthma, von Noorden found the eosinophile cells increased at the time of the attacks, *i.e.*, they amounted to ten per cent. or more of the white blood corpuscles. He believes, therefore, that a certain relation between the percentage of eosinophile cells and the occurrence of the asthmatic attacks is probable. By other authors, as, for example, Seifert, such an increase could not be demonstrated. In one case the latter found the percentage of eosinophile cells among the leucocytes to be not more than two, in another not quite three. But this question needs further investigation.

Complications, Terminations, and Prognosis.

Asthma may be complicated by various other affections, or it may run its course quite independently. The most frequent complication is bronchitis. During the existence of an acute bronchitis asthma often disappears temporarily, as is often observed when asthmatic patients are attacked by an acute febrile disease. But chronic bronchitis often remains as a sequel and residuum of asthma. Experience shows that complications of asthma by tuberculosis are extremely rare, but the one does not absolutely exclude the other. Of course,

we do not at once think of asthma if a tuberculous patient has attacks of dyspnœa. Dyspnœal and asthmatic attacks are two different things. Böngelmann reports the case of a woman with tuberculosis who suddenly had asthmatic attacks, which ceased at once after she had coughed up a caseated gland. In this case I do not think it correct to speak of asthmatic attacks, and the expression "pseudo-asthmatic attacks" should also not be used. They may have been attacks of dyspnœa, they certainly were not asthma.

Of other complications gout is especially to be mentioned. Arthritic and asthmatic attacks may alternate, or gout to a certain extent may take the place of asthma. In general, however, the complication of asthma by gout is rare. Sée found only fourteen arthritics in three hundred and seventy asthmatics; Lecorché, five asthmatics among one hundred and fifty arthritics. The relations of skin diseases and of epilepsy to asthma have already been noticed. Neuralgias of various kinds may sometimes alternate with asthma.

The course of asthma can never be certainly predicted. Apparent cures are often seen. The attacks may cease for years and subsequently recur. Especially in nasal asthma after local treatment of the nose a frequently long-continued cessation of the attacks has been observed, yet often enough they finally recur. This should not seem strange, for the cure of the nasal affection removed the exciting cause, not the predisposition to asthma. The favorable influence of a change of residence is often observed. In other cases the attacks grow gradually weaker spontaneously and finally disappear without our being able to say what factor has really effected the cure. The attack itself, however severe it may appear, ends favorably as a rule. Danger lies in the frequency of the attacks and the resulting exhaustion, but above all in the secondary consequences, especially the secondary pulmonary emphysema which is a not rare sequel of asthma. As a result of this, the well-known lesions of emphysema, secondary dilatation of the right heart, secondary changes in the kidneys, dropsy, etc., develop.

It is much more uncommon for asthma to be associated secondarily with pulmonary emphysema. It is true that in the latter disease the term "asthma" is often employed, especially by the patients, to designate an occasional increase in their shortness of breath, but this is rarely true asthma, but only a temporary dyspnœa which finds its cause and explanation now in an exacerbation of the catarrh, again in a transitory weakness of the heart, etc.

Chronic bronchial catarrh is also not an infrequent result of repeated violent asthmatic attacks. Bronchiectasis and putrid bronchitis are also, according to Leyden, not rare sequelæ of asthma.

The frequent irritation of the bronchi by the secretion of asthma leads, he thinks, to reactive catarrhs and even to dilatation of the bronchi. As a result of infection with the germs of putrefaction putrid bronchitis may develop, but the latter is not usually very obstinate and yields, generally in a short time, to suitable treatment.

Cures of asthma are frequent. But we can hardly fix positively the point at which we shall begin to speak of a cure, for the attacks may return after a cessation of years. Asthma is generally very obstinate. Of prognostic importance are the exciting cause, the duration of the attacks, the time of their commencement, and the age of the patient. In early youth cures are not infrequently observed. When the disease has lasted beyond the fortieth or forty-fifth year permanent sequelæ are probable. In general the prospect of cure is inversely as the duration of the disease. Complete cure is only to be expected when the respiratory and circulatory organs are quite intact. It is favorable for the prognosis if the attacks gradually diminish in frequency and intensity, especially if the patient is young. The causative factor is, above all, decisive in the prognosis. Many attacks are only excited by quite definite causes, certain kinds of dust or certain odors. The prognosis of such cases is favorable.

Mental influences also play an important part not only in exciting but in withstanding the attacks. Implicit confidence of the patient in his physician is, in many cases, an important condition of cure.

The Nature of Asthma.

No final answer can be given, even to-day, to the question as to the nature of asthma. Yet, in general, it is agreed that it consists essentially in spasmodic conditions within the respiratory apparatus, excited through nervous influences, although opinions still differ as to what portions of the respiratory organs are immediately attacked by this spasm. But besides this a series of questions still remains unsettled, such as that of the significance of Leyden's crystals and Curschmann's spirals.

We may pass by many theories, since they date from a time in which the term "asthma" was applied much more widely than it is to-day. Thus the view advanced by Sanderson that asthma is due to a paralysis of the muscles which open the glottis must seem at once inadmissible to every one who is familiar clinically with the symptomatology of asthma. Paralysis of the dilators of the glottis has not a single symptom in common with asthma. The view first suggested by Bean, which reappears from time to time, that asthma is simply a bronchitic dyspnœa also need not be discussed. If I ex-

pend a few words upon it, I do so because of the recent publications of Ungar, who, as the result of his very careful examinations of the sputum, has accepted this theory and believes that asthma should be regarded simply as the consequence of impermeability of the bronchi caused by changes in the mucous membrane and by the products of such changes, the spirals, and that it is therefore merely a manifestation of obstruction. In reply to this, I can only repeat the objection which I raised against this view years ago, namely, that the blocking of a greater part of the lumen of the bronchi by a gradually progressive swelling of the mucous membrane and by the accumulation of secretion may indeed cause dyspnœa, but can never alone produce the characteristic features of the asthmatic attack. The rapid onset of the attack, the sudden occurrence of the most extreme dyspnœa, and the often equally rapid cessation of the paroxysm lead us involuntarily to think of a nervous influence and of a spasmodic process. The fact, too, that the attacks are often excited suddenly through simply nervous influence, through psychical emotion, is hardly consistent with the supposition of an acute catarrh of the finer bronchi.

There are essentially three theories which have been adopted to explain the phenomena of the asthmatic attack.

The first theory is that in the asthmatic attack there is a swelling of the bronchial mucous membrane in consequence of dilatation of its blood-vessels by the vasomotor nerves (Weber, Störk). The second theory assumes a spasm of the diaphragm and perhaps of other inspiratory muscles. The third theory explains the phenomena of the asthmatic attack chiefly by a spasm of the bronchial muscles. Others again assume besides the spasmodic element simultaneous vasodilator processes in the smaller bronchi. Curschmann assumes for most, if not all, of the cases a definite disease of the bronchial mucous membrane, the so-called bronchiolitis exudativa, as the primary affection, which secondarily causes the bronchial spasm. Leyden, who also supports the theory of bronchial spasm, sees in the characteristic secretion first described by him the explanation of the mode of action of the bronchial spasm, which, according to him, occurs only in such bronchi as are choked by the viscid secretion.

The first of these theories, that a swelling of the mucous membrane and an abnormal secretion into the finer bronchi are caused reflexly through the influence of the vasomotor nerves, and that by this alone the phenomena of the attack are explained, has certainly much that is attractive. It explains many but, as it seems to me, not all the phenomena. It may explain the sibilant râles, the secretion of the bronchial mucous membrane, the expiratory dyspnœa,

and perhaps even, to a certain extent, the depressed situation of the diaphragm, but it cannot explain the sudden onset nor the sudden disappearance of the attacks. I cannot agree fully with Einthoven, who rejects this theory because experiments upon animals showed that disturbances of the circulation, and even sudden and great changes in the blood pressure, produced no, or only slight mechanical impediments to respiration; it is certain that the secretion of the bronchial mucous membrane also plays a certain part in man. The prompt effect of narcotics does not harmonize with the supposition that an impediment of the breathing due to the action of the vasomotor nerves is the only cause of the dyspnœa. That in certain forms of asthma vasomotor changes, vascular hyperæmia, and swelling of the mucous membrane play a not unessential part is shown, for example, by hay asthma which generally begins with coryza and other phenomena of irritation, as well as by many other forms, especially nasal asthma. These symptoms alone do not constitute asthma, yet it is easy to see that processes similar to those in the nose may play a part upon the bronchial mucous membrane in asthma. But of course such a swelling of the mucous membrane of the smaller bronchi and of the bronchioles, even if it be extreme, does not suffice in itself to produce the complexus of asthmatic symptoms.

This second factor, which is necessary to complete the picture of asthma, some have sought in a spasm of the bronchial muscles, others in a spasm of the diaphragm. Before I enter upon the question whether the spasm is of the bronchi or of the diaphragm, I would emphasize the point that the almost constant presence of a peculiar secretion, which has been proved by Leyden and Curschmann, should receive attention in constructing the theory of asthma. It may be disputed whether the bronchiolitis exudativa, as Curschmann has named it, represents simply a predisposing factor, or whether, as many others think, it is a coincident or secondary process; one of these two rôles must be conceded to it. That the bronchiolitis exudativa alone is not sufficient to produce typical asthma has been thoroughly demonstrated by Curschmann himself. He has expressly insisted that the bronchiolitis is not to be regarded as identical with asthma, but only as an affection which causes it with especial frequency, indeed almost constantly. On the other hand, it has been found that Curschmann's spirals and Leyden's crystals are found also in cases which are decidedly to be regarded as instances of nasal asthma, and that in these cases, if the asthma is cured by treatment of the nose, the sputum subsequently disappears and with it also the spirals and crystals. Many are therefore inclined to regard the peculiar sputum of asthma only as a consequence or

accompaniment of that disease. According to this view the "spiral bronchiolitis" does not play the part of a predisposing or exciting cause, but is simply an important symptom which belongs directly to the disease itself.

With respect to the spasmodic element of the asthmatic attack, the defenders of the theory of spasm of the bronchial muscles, which has been maintained especially by Biermer, start with the assumption that the office of the bronchial circular muscles is to diminish the lumen of the bronchi. If this is correct—and there is no reason for thinking otherwise—we must ascribe to the bronchial muscles an expiratory action in the sense that they assist the elastic fibres of the lungs in their resistance to the negative pressure of inspiration, that they therefore are in this sense antagonists of the inspiratory muscles.

Attempts have been made to investigate experimentally the function of the bronchial muscles. By stimulation of the vagi contraction of these muscles has been induced, but the increase in pressure thus caused was so surprisingly small, as my experiments showed, that no certain support could be gained for the theory by the experiments. I never succeeded by means of direct stimulation of the vagi in producing such a contraction of the bronchi as would seem necessary to explain the emphysema of the lung. Yet it appeared that stimulation of the vagi did cause a pulmonary emphysema, if not directly, then indirectly by the way of a reflex stimulation of the phrenic nerve. Although I had always been inclined to favor the theory of bronchial spasm and had formerly supported it, yet at one time because of these experimental results I felt compelled to say that no support for the theory of bronchial spasm had been derived from the results of physiological experiments, which spoke rather in favor of spasm of the diaphragm. I am happy to be able to say to-day that the gap which was still left after my experiments and those of earlier investigators has now been filled. I by no means underestimate the importance in this direction of the objections which have been raised, especially by Biermer, against the theory of spasm of the diaphragm, but they were only theoretical objections, and were seemingly opposed by the results of experiment.

But since then Einthoven, by means of experiments by a new method which are not open to criticism, has shown directly the powerful action of the bronchial muscles. The new method which Einthoven pursued in his investigations is as follows: A constant volume of air is blown into the lungs by a syringe, the piston of which is moved up and down by the eccentric of a wheel turned at a regular speed. The intrapulmonary pressure is measured simulta-

neously by a resisting manometer, which by means of an especial mechanism comes into free connection with the lungs only for a moment at a time during a definite period of respiration. With this apparatus a narrowing of the bronchi must manifest itself by an increase in the resistance to be overcome by the blown-in air, and the measuring manometer must consequently register by its float an increase of pressure. This ingenious apparatus, as the curves which it produced show, gave accurate and unmistakable results, with respect to the narrowing of the bronchi through stimulation of the peripheral ends of the vagus, which were surprising. By stimulating the vagus Einthoven succeeded in obtaining an increase in respiratory pressure of more than 120 mm. of water, and by poisoning the animal with carbonic acid gas, one of more than 175 mm. of water. By this it appears to me that the former objections to the theory of bronchial spasm are removed.

That by a spasm of the bronchial muscles, especially if we suppose certain changes also in the mucous membrane, all the phenomena of the asthmatic attack can be satisfactorily explained is no longer to be doubted after these experiments. The development of an acute pulmonary emphysema, which we constantly find in the asthmatic attack, presupposes a strengthened inspiration and an impeded expiration, especially the latter. Such an emphysema occurs when obstacles are present in the smaller air passages, which are more easily overcome in inspiration than in expiration. The patient then draws in during inspiration more air than can escape during expiration, and the lung must therefore become distended. But the spasm of the unstriped muscular fibres of the bronchi must present such an obstacle, and thus are satisfactorily explained the acute pulmonary emphysema and the preponderatingly expiratory dyspnœa of the asthmatic.

The sibilant râles of the asthmatic attack point unmistakably to obstacles in the smaller bronchi. They cannot be caused by a spasm of the diaphragm; for their explanation we must suppose local impediments to the movement of air in the smaller bronchi. These might occur in a bronchial spasm or in catarrhal fluxions or swollen states of the bronchial mucous membrane. That the latter play a part in asthma is shown by the secretion of the mucous membrane. Hence I believe that the theory of spasm of the bronchial muscles is the correct one, although in very severe attacks a spasm of the diaphragm also seems to me more than probable.

But changes of the mucous membrane play a not unimportant part in asthma, as the almost constant occurrence of sputum containing spirals and crystals proves. That they alone are not sufficient to ex-

plain the phenomena of asthma, as is Weber's theory, I have already shown above.

But the connection with each other of the individual symptoms can be and has been thought of in various ways. Leyden, who ascribes the chief importance to the crystals, not to the spirals, in the sputum, thinks that the bronchial spasm is secondary. Curschmann distinguishes cases of asthma with normal and with diseased lungs. The latter, according to him, is especially frequent; he supposes that in this form a chronic disease of the mucous membrane of the finer ramifications of the bronchi is present, for which he proposes the name "bronchiolitis exudativa." He conceives of bronchiolitis exudativa as an independent disease which is not to be absolutely identified with bronchial asthma but which (in its chronic, not its acute form) practically always leads to the latter.

But the opposite view has also been maintained, in fact it seem to me that the majority is inclined to that view, viz., that the characteristic sputum containing spirals is rather the consequence of asthma or of an acute disease of the bronchial mucous membrane which accompanies asthma. Curschmann, on the other hand, thinks that bronchiolitis exudativa is a peculiar form of disease which has nothing in common with an ordinary catarrh, and further that in every single case the persistence of the bronchiolitis can be demonstrated even during the intervals between the attacks. Curschmann regards it as incorrect to consider, as many do, that the "spiral bronchiolitis" is merely a secondary affection dependent upon nasal affections, since cases of bronchiolitis without nasal disease as well as cases of severe nasal asthma without bronchiolitis are met with. The objection properly made to this view, that cases are observed in which the spirals have disappeared after an operation upon the nose, Curschmann answers by inquiring as to the duration of the cure and the frequency of such cases. Although Curschmann reports cases in which after radical operations upon the nose the spiral bronchiolitis either did not disappear or returned after some time, yet even this does not finally settle the question. Curschmann himself finally prudently declares that as yet he has not definitely determined his position with regard to those questions.

Confining ourselves for the present to ascertained facts, we may regard it as established that on the one hand nasal asthma and bronchiolitis exudativa occur frequently together, that on the other hand cases of nasal asthma without bronchiolitis are certainly very rare, and that often the crystals and spirals disappear when the asthma has been cured by treatment of the nose.

As I pointed out at the Congress for Internal Medicine in 1885,

only long-continued accurate investigations of the sputum, not only at the time of the attacks but in the intervals, can make clear the rôle of spiral bronchiolitis in asthma. Unfortunately even the more recent investigations in this direction have afforded results of little value. Only when the sputum is carefully examined in every case of asthma, not only of nasal asthma, but also of other kinds of asthma, and not simply during the attacks but also in the intervals, can an elucidation of this question be expected. Such investigations have rarely been undertaken. Lewy has made a considerable number of them in twenty-six cases of asthma. In all the cases during a period of complete remission neither crystals nor spirals were to be found, but they invariably appeared as soon as asthmatic attacks even of slight intensity developed. We may assume that this result, which has been confirmed by others, will be still further corroborated. In my opinion a direct connection, or at least a coincidence of asthmatic attacks with the appearance of the sputum containing spirals, may now be regarded as proven. Curschmann says he has observed the persistence of the bronchiolitis after the cessation of the asthmatic attacks, but that does not at all contradict this view. The bronchiolitis may continue for a time notwithstanding the absence of the attacks. And again, although in isolated cases the bronchiolitis continues in spite of the cure of the asthma, that fact by no means proves that the bronchiolitis must have been the primary affection. The sputum of the bronchiolitis need not necessarily disappear at once after the attack. That spirals are occasionally observed under other circumstances without leading to asthmatic attacks proves nothing with regard to the present question. Every swelling of the nose does not necessarily cause asthma nor need every bronchiolitis exudativa. Still less importance need be assigned to the observation that asthma occurs without the spirals. Aside from the fact that this is only exceptional, a negative result proves very little, especially as spirals and crystals are easily overlooked unless the search is most carefully conducted.

A fact just made known by Cahn seems to me to be not without importance as regards the connection between affections of the nose and those of the bronchial mucous membrane. Cahn has shown that there are cases of acute and even of chronic bronchitis which are to be referred to disease of the nose and which are immediately cured by the cure of the latter. In several cases he succeeded by the removal of polypi which by no means completely obstructed the nasal passages in curing at once obstinate bronchial catarrhs.

That the crystals as such do not excite the attack, as was formerly supposed, is apparent from the fact that they are, as it were, wrapped

up and hidden in the plugs of the sputum so that they hardly touch the bronchial mucous membrane. Moreover, there is no relation between the amount of crystals present and the attacks. The crystals have also been found by Pfuhl in simple bronchitis without asthma.

The spirals are in general to be regarded as the product of a catarrhal desquamative process in the finest bronchial tubes. The coincidence of the sputum containing the spirals with the asthmatic attacks and the disappearance of the spirals with their cessation denotes a more than simply predisposing or accidental connection of the spiral bronchiolitis with the asthma. If, in isolated cases, after the attacks have continued for a long time, spirals are found occasionally in the intervals, that fact is not opposed to such connection. A positive decision of these questions can, however, only be reached after long-continued examinations of the sputum in the most various forms of asthma. The results of investigations hitherto permit us to formulate no positive answer, although, for the reasons mentioned, the view as to the connection which has been presented must be regarded as the most probable one.

Diagnosis.

The name "asthma" is often misused. Every rapidly developing dyspnœa is called asthma by the laity; but physicians too, not infrequently, apply the name incorrectly. Asthma is an especial form of suddenly developed dyspnœa. To asthma belongs the paroxysmal, preponderatingly expiratory, dyspnœa with acute pulmonary emphysema and sibilant râles. The expectoration of the asthmatic is also of diagnostic importance; it may, however, be absent occasionally at certain stages. But the characteristic constituents of the sputum will hardly ever be found wanting in careful search, especially in the later stages.

It is further characteristic of asthma that anatomical changes in the lungs and the heart which would explain the sudden dyspnœa are wanting. An occasional increase in the respiratory embarrassment of patients with emphysema and chronic bronchitis does not constitute asthma. A simple exacerbation of the catarrh may lead to an increase in the already existing impediments to respiration, but we should not be justified in speaking of a complication with asthma in these cases. It is true that genuine asthmatic attacks may supervene upon emphysema, but the attacks should be regarded as asthmatic only when the above-mentioned characteristics of the asthmatic paroxysm are present and when the sudden dyspnœa cannot be explained by a rapid increase in the catarrh or by other demonstrable changes.

Above all, the expiratory character of the dyspnœa is to be noted. Expiratory dyspnœa occurs only in emphysema and chronic bronchitis besides asthma. Einthoven's statement, based on theoretical grounds, that in the typical asthmatic respiration the inspiration is deep and strong and the expiration superficial and weak, does not correspond with the clinical picture. It is clear that inspiration also must be impeded though not as much as expiration, the impediment manifesting itself especially in a prolongation of that portion of the respiratory act.

Although it is stated by some authors that expiratory dyspnœa is observed when foreign bodies are present in the bronchi, yet this must be regarded as exceptional, and in this condition all the other symptoms have so little resemblance to those of asthma that it is hardly likely that they could be confounded with the latter. Confusion with spasm of the glottis, with paralysis of the dilators of the glottis, with tracheal tumors, and other similar affections is easily avoided. The mere inspiratory character of the dyspnœa in such cases shows that the obstruction is situated high up in the large air passages. Spasm of the glottis is most frequently confounded with asthma. But aside from the inspiratory character of the dyspnœa, the acute emphysema, the sibilant râles and the peculiarities of the expectoration are wanting. On the contrary, in this affection the thorax may even be drawn in during inspiration. Spasm of the glottis begins suddenly, lasts only a short time, at most a few minutes, and ends suddenly. The asthmatic attack may begin suddenly and rise rapidly to a maximum, but it always continues much longer than the spasm of the glottis, generally for hours. A confusion of spasm of the glottis with asthma is impossible for the even moderately careful observer.

But the latter disease may be more readily confounded with the rare neuroses of the vagus, which produce acute pulmonary emphysema—such cases as I was the first to describe, through my former assistants, Tuczek and Kredel. Up to that time in affections of the vagus attention had been paid almost exclusively to the disturbances of the heart's action, and the stenocardiac symptoms had been explained solely by such disturbances. In our cases, together with a very greatly accelerated action of the heart there occurred paroxysmally an acute pulmonary emphysema with dyspnœa. But this dyspnœa had in no way the characteristics of expiratory dyspnœa, and by this fact alone, aside from the extreme acceleration of the heart, it can be easily distinguished from genuine asthma.

In contrast with true asthma nervosum, or asthma bronchiale, a cardiac asthma is also spoken of. While in nervous or bron-

chial asthma a spasmodic condition affecting the respiratory apparatus is assumed, in cardiac asthma the essence of the affection is a disturbance of the activity of the heart. Here, as in bronchial asthma, the dyspnœa is the most prominent symptom, but it is not, as in the latter, a preponderatingly expiratory, but a mixed dyspnœa; the expiration and the inspiration are equally impeded. Corresponding to the insufficiency of the left ventricle, the pulse in it is as a rule small and accelerated. Moreover, in this the sibilant râles of bronchial asthma and the peculiar asthmatic expectoration are never observed. In this condition there is danger of an acute œdema of the lungs, which is never present in bronchial asthma. And the so-called cardiac asthma occurs only in patients in whom the heart is not sound, whether in consequence of disease of the heart itself or because of the presence of arterial sclerosis, contracted kidneys, or the like. With the help of these points of difference and with a moderately careful observation of the phenomena of the attack it should, as a rule, be easy to discriminate the genuine from cardiac asthma.

Finally, spasm of the diaphragm should be briefly noticed. This condition may also cause sudden dyspnœa. In chronic spasm of the diaphragm inspiration takes place spasmodically and with relative rapidity, the thorax then remains several seconds in this position of forced inspiration, after which there succeeds a rapid and forcible expiration. This is followed by another forced inspiration, by a fixation of the thorax in the inspiratory position, and then again by a short forced expiration. This is the clinical picture of clonic spasm of the diaphragm which is especially observed in the hysterical. A confusion of this condition with the complexus of symptoms of asthma is hardly possible.

I do not need to enter here into details with regard to the tonic spasm of the diaphragm, since I have already mentioned it in discussing the theories of asthma. I will only briefly touch upon an objection which has been raised against the theory of diaphragmatic spasm, which is, that a long-continued spasm of the diaphragm is inconceivable, since suffocation must result. It is easy to convince one's self experimentally of the incorrectness of this assertion at any time by stimulating the phrenic nerve. The assertion, which has been repeatedly made, that in tonic spasm of the diaphragm all movements of the lower edges of the lungs are prevented, is also incorrect. Changes of tension in the abdomen must result in movement of the diaphragm, however much it may be contracted.

An hysterical asthma has also been distinguished. Here there is generally a confusion with hysterical dyspnœa. But the latter never

resembles an asthmatic attack. When asthma occurs in an hysterical patient, its exciting cause must be sought for, as in all asthma.

Diabetic and uræmic asthma have nothing in common with genuine asthma. We should accustom ourselves not to speak of asthma in every case of sudden dyspnœa, but to employ this designation only when the above-mentioned characteristics of asthma are present. These last-named forms belong rather to cardiac asthma. It would be better to give up entirely the term cardiac asthma, since in it asthmatic symptoms are completely absent, the symptoms of cardiac dyspnœa only presenting themselves.

Treatment.

In hardly any other form of disease has the secret-remedy abuse attained such proportions as in asthma. But the reason of this is not, as Brügelmann thinks, "that the nature of the disease until a few years ago has been wrapped in impenetrable darkness," but that all kinds of dyspnœal states have been, and often still are, jumbled together under the name of asthma. That with such an extension of the conception of asthma remedies of the most diverse sorts might be recommended, and that now this, now that, remedy might prove beneficial, can hardly excite surprise. It has long been scientifically established what complexus of symptoms we are to call asthma, although with reference to the mode of production of the individual symptoms many points are still debated.

But the task which falls upon the physician in the treatment of asthma has long been known. If, as is so frequent in asthma, one has successes where the other has failures, the fact is not hard to understand. The principles of treatment of a certain disease may be established, but in the individual case it is the patient who must be treated. Asthma is a complexus of clinical symptoms, which manifests itself by spasm; it is a neurosis. At the bottom of this lies an especial predisposition, an especial irritability within the distribution of individual nerves. But the excitation can come from the most various parts, now from the nose, now from the throat, now from the genital organs, now from psychical excitement, etc. For that reason there can be no remedies which are equally efficacious for all cases. The treatment must be varied in accordance with the nature of the exciting cause and the physical condition of the patient. Of course here, as everywhere in practical medicine, experience teaches us many valuable lessons.

The object of therapeutics is twofold: first, to cut short, to do away with the individual attack; second, to prevent the recurrence of

the attacks. For both these objects a large number of remedies and methods are at command.

Let us first consider the remedies which are to be employed when the attack has already developed. Here the first efforts are directed towards shortening and mitigating the attack. Of course in a dyspnœal attack of any kind fresh and pure air must be provided before all things else. The windows should be opened, constricting articles of clothing should be at once removed. Generally the patient has already done this long before the physician reaches him. Nor does the physician need to indicate to the patient the posture which most facilitates his respiration; the patient finds out instinctively the attitude which affords him the most relief.

Since asthma depends upon a spastic process it is natural to employ antispasmodic and narcotic remedies for the attacks. In fact nothing helps so quickly as a hypodermic injection of morphine. When the attack is very violent, it is best to have recourse at once to this; after a short time the spasm begins to relax and the patient's breathing is much relieved. There is of course the danger of producing the morphine habit in cases in which the attacks recur very frequently. Upon the recommendation of Biermer chloral hydrate has been much used, and, it cannot be denied, with satisfactory results. Its quieting effects are generally seen very soon after its administration. Upon the ground of my own experience I can warmly recommend chloral hydrate, although I prefer morphine subcutaneously injected in especially violent attacks.

Of other remedies nitrite of amyl, nitroglycerin, and sodium nitrate are to be mentioned. Nitrite of amyl has been especially recommended by Pick. I myself, after repeated use of this remedy, have seen a slight diminution in the dyspnœa but never a complete disappearance of the symptoms of the attack, never so prompt an effect as from the employment of morphine and chloral hydrate. Fraser recommends sodium nitrite and nitroglycerin as the most trustworthy remedies.

Chloroform and methylene bichloride have also been recommended. But both of these share with those mentioned above the disadvantage of transitoriness in their effects. Demme recommends bichloride of methylene, especially for children, inhaled in doses of from eight to ten drops, either pure or mixed with chloroform, and says that it affects the circulation less than other anæsthetics. Some claim to have seen relief from ethyl iodide inhaled in doses of ten to fifteen drops from blotting paper or linen. Inhalations of ether have also been advised.

For a long time preparations of belladonna and cannabis indica

were used in the treatment of the asthmatic paroxysm. To-day morphine and chloral hydrate are generally used in their place. Subcutaneous injections of atropine have been recommended by a few as effective in the asthmatic attack.

Hypodermic injections of cocaine have been advised by Beschorner, Mosler, and others. It would appear to be of more importance to make a local application of cocaine in those cases in which the point of excitation of the attacks is situated on an easily accessible mucous membrane. This applies especially to hay asthma and to other forms of nasal asthma.

Mays recommends strychnine and atropine. He begins with $\frac{1}{30}$ grain of strychnine and $\frac{1}{150}$ grain of atropine, and increases the dose to $\frac{1}{20}$ grain of strychnine and $\frac{1}{100}$ grain of atropine, then gradually diminishes the dose again. It has also been advised to inject hypodermically the hydriodate of hyoscine in the dose of $\frac{1}{4}$–$\frac{1}{3}$ mgm.

Poisonous plants belonging to the family of the Solanaceæ have long enjoyed an especial reputation in the treatment of asthma, the smoke from their burning leaves being inhaled. Stramonium and belladonna leaves are most used. The dried leaves are smoked either by themselves or mixed with tobacco in a pipe, or are rolled in paper and smoked as cigarettes. The leaves may also be burned in the patient's room. In the latter case the leaves may be impregnated with a solution of nitre to increase their inflammability. Sometimes the attacks are cut short by ordinary tobacco smoke, but such a result occurs only occasionally and only in patients who are not smokers. But stramonium cannot be regarded as a reliable remedy. To increase its efficacy it has therefore often been combined with other solanaceous leaves. The "cigarettes Espic" are very widely used. Their formula, according to Trousseau, is as follows:

℞ Fol. elect. herb. belladonnæ,	0.36
Fol. elect. herb. hyoscyami,	0.18
Fol. elect. herb. stramonii,	0.18
Fol. elect. phellandrii aquat.,	0.06
Extract. opii,	0.008
Aq. laurocerasi,	q.s.

The leaves, well dried and freed of their ribs, are cut up and carefully mixed. The opium is dissolved in cherry-laurel water and the mass is uniformly dampened with the solution. The paper which is used in making the cigarettes is also previously washed in a maceration of the leaves above named in cherry-laurel water and carefully dried. The patient smokes one or two of such cigarettes during an attack.

The burning of paper containing arsenic or nitre has also been

recommended by many. For the former a sheet of unsized paper is soaked in a solution of 1 gm. potassium arsenate in 15 gm. of distilled water, is then dried and cut into pieces. The nitre paper is prepared in a similar way. Blotting paper is soaked in a half-saturated solution of nitre, and is then cut into smaller pieces and rolled into the form of cigarettes. How these remedies act cannot be positively explained. The experience with them is that in some cases they bring relief, and in others fail entirely.

Of the other numerous compounds for smoking and inhalation, many of which, in the form of secret remedies, have been much lauded, I may mention especially Wiesenthal's asthma powder, recommended by Drobner, which consists of nitre and stramonium and belladonna leaves. It is used for fumigation. Gerard's remedy is a cigarette consisting of belladonna leaves and stramonium, impregnated with a solution of nitre and of the seeds and capsules of the black poppy. Sée recommends especially the pyridins. According to him these are the active factors of the manifold asthma cigarettes and asthma powders for fumigation. In these compounds they are mingled with many useless and injurious substances so that the use of the pure pyridins is to be recommended. Plicque advises that pyridin should never be directly inhaled, but that, for a room of the capacity of about 20 c.m. 4 gm. should be permitted to evaporate, the room being aired after half an hour at the longest. Favorable results have also often been observed from the inhalation of solutions of menthol.

Much use for a long time, particularly in France, was made of the procedure first advised by Ducros of brushing the pharynx with ammonia. But this method proved to be not without danger, hence inhalations of ammonia were resorted to, a phial filled with ammonia being held beneath the patient's nose. The method proposed by Faure, to pour a tablespoonful of ammonia into a saucer and have its fumes inhaled from a little distance, is preferable. Trousseau recommends that the patient's nostril be stopped with cotton during the inhalation. The fact that many asthmatics find themselves improved in health in localities where ammonia is developed, as has been frequently observed, speaks in favor of the good effects of ammonia, in some cases of asthma at least. Trousseau tells of a sea captain who had no trace of asthma as long as he was upon his ship which was laden with guano, or was on the islands where guano is obtained.

Emetics, especially ipecacuanha, have also been recommended. In my opinion they are to be used only exceptionally, as perhaps in children in whom there are symptoms of a severe bronchitis. Cursch-

mann states that he has used strong infusions of ipecacuanha in protracted attacks of asthma with the best results. Emetics are contraindicated in elderly people.

Inhalations of oxygen have also been recommended. In very severe attacks they can hardly be administered; in milder attacks a trial may be made of them. The difficulty of obtaining the oxygen apparatus will, however, interfere with the general use of this gas.

Inspirations of compressed and expirations into rarefied air have also been employed; but although this method has given benefit in some cases during the free intervals, in the attack itself it is hardly ever applicable, and moreover the apparatus is generally not at hand.

The local application of the induced current has been suggested as a means of cutting short the asthmatic attack. Schäffer especially commends its effect; he states that he has repeatedly seen violent asthmatic attacks disappear, as if by magic, after its use. According as he believes that the location of the exciting cause is in the upper or the lower portions of the nerves, he places the electrodes under the angles of the jaws or at the level of the thyroid cartilage. Bresgen, Fraenkel, and others also claim a certain favorable effect from the faradic current.

The preceding are the most important remedies for the attack itself. Of course this list does not comprise all the remedies which have been advised, for a full enumeration of them is scarcely possible. But our attention should be directed here to one of the exciting causes, the psychic. In many cases the attacks occur irregularly without demonstrable cause; in other cases they occur as the result of certain definite stimulations. I have already mentioned a case above in which the asthma was excited by the odor of a rose, but in which it also occurred when an artificial, instead of a natural rose was held before the patient. Here the idea of the irritant acted in the same way as the irritant itself. We often see that the attack is caused by psychic emotion. Sometimes even the fear of an attack is sufficient to excite one. It may be anticipated in such cases that suggestive treatment will suppress the attack. But suggestive therapy plays a more important part in the prevention of the paroxysms and in the treatment of the predisposition to asthma than in combating the individual attack.

The second indication in the treatment of asthma is the prevention of the recurrence of the attacks. As we have already seen, two factors play a part in the production of asthma. The one is the immediate exciting cause of the attack, which is situated sometimes in the nose, sometimes in the throat, sometimes in the sexual system, etc. The

second is the predisposition, the abnormal excitability of the nerves. Experience has shown that the removal of the first factor, *i.e.*, the cure of the local malady, results in the disappearance of the asthma for months or even years. But often it is found that although the local disease, of the nose for example, has been completely cured, yet the asthma returns after an interval. This is not strange. If it appears for example that from a circumscribed swelling in the nose, the mucous membrane covering the turbinated bones or elsewhere, a reflex, that is, an asthmatic attack, is excited, and if we cure this diseased spot by cauterization or other means, henceforth asthmatic attacks will no longer be excited from that point. But the predisposition to asthma, the peculiar state of the nervous system, remains unchanged. Hence it is not surprising if the attacks recur subsequently. Not very rarely we see that there are several "asthma points," that asthma is excited from different parts of the body. The facts are similar with regard to other organs. When there is a predisposition to nervous cramps of the stomach or to migraine, we see in some individuals that these affections regularly appear after emotional excitement, after anger, and after mental overwork; but we also sometimes see them develop from other causes; that is, the excitation of the attacks may travel by various paths, and just so it is with asthma. The second indication for treatment mentioned above is therefore twofold. A most careful search should be made for the point of excitation, and if one be found that source must first be removed. But in the second place—and this is the more important—the nervous predisposition to these spasmodic attacks should be combated.

It must be regarded as a long step in advance that the fact has been recognized that asthmatic attacks are very often excited from the nose and its adnexa, more frequently through the trigeminus than through the olfactory nerve. Of course patients, who get their attacks from smelling hay, flowers, ipecacuanha, etc., should be advised to keep away from these sources of irritation. But at the same time a careful examination of the nose, the nasopharyngeal space, the pharynx, and the larynx must be instituted and with the aid of cocaine a search should be made for asthma points. If a morbidly excitable spot is found, it may be subjected to local surgical treatment, and thus the abnormal stimulation of the nerves which are distributed to the parts will be abolished. But with the local treatment that of the general condition should never be neglected.

Of course only a very careful and minute search for painful points, from which the attacks are excited reflexly, will be successful. All the other organs must be submitted to a thorough examination in the

same way as the nose. But too great confidence should not be placed in the treatment of the nose. It is well known that the good results have been much exaggerated. Some have gone so far in their zeal as to regard almost every case of asthma as one of nasal asthma, and so for a time it was the fashion to burn with acids or the cautery the nasal mucous membrane of every asthmatic. Now that the excitement has subsided, it is seen that the nasal treatment has often been of no benefit, or has efforded but temporary relief. Nevertheless, the examination of the nose should be neglected in no case of asthma, unless the exciting cause is already known with absolute certainty, and if abnormalities are found, if it appears that reflex phenomena follow when the sound is pressed upon certain definite spots, local treatment by a skilful specialist should be instituted.

I have already mentioned above that many attacks occur only under certain conditions. Thus there are cases in which the attacks are connected with pregnancy and cease after delivery. In some cases a simple change of residence is sufficient to stop the attacks, without its being possible to determine the reason why the former dwelling-place was injurious. For many patients life in a different climate is enough to cause a cessation of the attacks. It has even been affirmed that there are localities the climate of which can be regarded as conferring immunity upon asthmatics. This is by no means universally true. It is well known that many patients experience a considerable measure of relief after a stay of some duration in high altitudes. But the altitude alone is not the cause of this. If asthma is observed more rarely in some places than in others, this fact by no means proves the existence of an immunity. Asthma is an affection which occurs everywhere, from which no climate confers absolute immunity.

It cannot be doubted that asthma may be excited from the uterus and its appendages as well as from the male sexual organs. With regard to many of these cases it can indeed be said that they were not true asthma, but dyspnœal attacks, often hysterical dyspnœa or hysterical anxiety. Peyer, especially, has reported cases which prove that asthma may develop as the result of long-continued masturbation or of spermatorrhœa. Thus, to give one example, he reports the case of a country gentleman twenty-six years of age, who was also seen by Biermer. This patient had his first asthmatic attack in his eighteenth year, and the attacks recurred about four times in the next two years. In the following four years the patient, who now devoted himself zealously to agriculture, enjoyed perfect health. Then he married and assumed the charge of a hotel. He ascribed the fact that he did not feel so well as formerly to the lack of the

exercise in the open air to which he was accustomed. Some catarrh and the former asthmatic attacks again appeared. A stay of two months in Davos removed the catarrh and stopped the asthmatic attacks, but the latter recurred after his return to his home. A second visit to Davos produced again a temporary cure. But soon afterwards the attacks returned and became increasingly more severe. A long course of iodide of potassium prescribed by Biermer gave at first a little relief, but soon the attacks began to occur with frightful rapidity. A remark let fall by the patient after an attack, that it seemed to him that coitus was injurious to him, since after it he was almost certain to have an asthmatic attack, led Peyer to inquire more closely into the sexual life of the patient, when it appeared that the patient had masturbated since childhood and frequently had discharges of semen without erection. A local treatment of the spermatorrhœa, consisting in the use of sounds and astringent injections, completely cured the asthma.

Peyer reports several similar cases. Of course we must be careful about applying the designation "asthma" to such cases and employ the term only when there are really typical asthmatic attacks. When such a cause is discovered, the appropriate local treatment must be instituted. This is equally true of diseases of the female sexual organs, provided that a connection between these and the asthmatic attacks can be demonstrated. For of course the two forms of disease may be present at the same time, and yet be independent of each other.

Of internal remedies which have been recommended for asthma iodide of potassium (or sodium) is unquestionably the most important. This is also the active constituent of many of the secret remedies which have been used, as, for example, in that of Aubrée, which was valued highly at one time. Its administration is sometimes attended with difficulties on account of its well-known unpleasant effects, but these can generally be overcome if one begins with quite small doses and passes slowly to the larger doses. To produce the desired effect the medicine must be given for a considerable time and in large doses 1.5, 2, or 3 gm. (gr. xxij.–xlv.) a day. Its bad taste is best corrected by taking it in milk. The addition of syrups is not to be advised, but peppermint water may be used to conceal the taste. It is true that it may fail in some cases, but in the majority a certain improvement is produced; sometimes the results are excellent. If some dispute the efficacy of iodide of potassium, the explanation must be either insufficient observation of the cases or the fact that the drug was given for too short a time and in too small doses.

All the other internal remedies which have been recommended are

in my experience far inferior to iodide of potassium, although they may have proved efficacious in isolated cases. Ruhemann has very recently recommended in place of iodide of potassium the iodate of sodium, one pill of 15 cgm. (gr. iiss.) to be taken three times a day for a considerable time. He regards the especial advantage of the iodate of sodium to be that, in contrast with iodide of potassium, it does not at all affect the appetite. I have no personal experience with it. The citrate of caffeine is warmly recommended by Skerritt. Arsenic is the most important of the other remedies. Lebert recommends the use of this in obstinate cases in connection with quinine and atropine. Quinine has also been repeatedly and strongly recommended. Other remedies to be mentioned are: nitrate of silver, oxide of zinc, bromide of potassium, tincture of lobelia inflata, hyoscine, castoreum, camphor, and tincture of valerian. To most of these an other than a suggestive action can hardly be ascribed.

Inhalations of sodium chloride and sodium bicarbonate, each 1 part in 200 of water, twice a day, have been advised by Leyden, not as a directly curative remedy, but as an adjuvant.

Flowers of sulphur, recommended by Duclos as "a therapeutic agent of infinite efficacy" to prevent the return of asthmatic attacks, has not been received with favor in spite of this strong advocacy.

With regard to the pneumatic method, it may be said that its value is not yet thoroughly determined. This method is applied partly with the portable apparatus, and partly with the pneumatic cabinet. While at first great things were expected of it, the conviction has gradually gained ground that, though it may often bring relief and effect improvement, it is as yet not directly curative. As already mentioned, it is hardly possible to employ a pneumatic apparatus during the attack itself. In the intervals of the attacks the pneumatic apparatus has the advantage that it strengthens the lungs, and that it affords a kind of pulmonary gymnastics. The pneumatic cabinets are preferable to the pneumatic apparatus; but with regard to their value also opinions are divided. A genuine cure is probably hardly ever produced by them. Their favorable effects depend chiefly upon their influence over the catarrh and the secondary or accompanying emphysema.

The use of the respiratory chair invented by Zoberbier-Rossbach has the same disadvantages as the pneumatic method. During the attack itself it cannot be employed; in the intervals there is no occasion in uncomplicated cases of asthma to use an apparatus to assist expiration, since in such cases the patient is free from discomfort. Such an apparatus is of value only in cases in which an emphysema is also present, as a remedy not for the asthma, but for the em-

physema. The same objection applies to the corset-like contrivances of Schreiber and Feris, to the respiratory girdle (*Athmungsgürtel*) of Steinhoff, to Göbel's respiratory chair with automatic compressor, and to Traub's compression apparatus. The object of all these forms of apparatus is to assist expiration, by compressing the thorax during expiration. During the attack such apparatus cannot be applied; in the intervals they are not required except in cases in which the expiration is still impeded, when emphysema is also present.

The object of the methods of cure hitherto mentioned is essentially to cure the diseased spot from which the excitation of the individual attacks proceeds. The primary cause, the predisposition, is not thereby changed. But cases are not rare in which the mere idea that an asthmatic attack may be impending is sufficient to cause one. Here a psychic, a suggestive treatment is needed and is often of benefit. The vigorously given suggestion of the physician, that an attack will not occur if the patient has implicit confidence in him, will often prevent the attack. The main end to be kept in view in the treatment is, however, to quiet the abnormal excitability of the central nervous apparatus. No remedy will do this directly. We do not know upon what this abnormal excitability depends, and hence we are ignorant of the way by which it can be removed. We can approach the goal only indirectly: at one time by suggestion, at another by strengthening the general nervous system, by hardening the body, etc. We proceed here on the same principles as when we seek to strengthen the nervous system in hysteria and neurasthenia. The general condition is above all to be regarded. Regulation of the diet and of the whole mode of life plays an important part in the treatment of asthma. Respiratory gymnastics, hardening processes of every kind, and hydrotherapeutic procedures are to be employed. Of course such treatment can be administered to better advantage in a sanatorium than at the patient's home.

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HAY FEVER.

BY

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HAY FEVER.

Synonyms.—Hay asthma, rose cold, June cold, autumnal catarrh, rhinitis hyperæsthetica, catarrhus æstivus. The term hay fever is generally used to designate the disease when it occurs in the fall months in contradistinction to similar affections that are not infrequently observed in the winter, spring, and early summer.

Hay fever is one of the neuroses the symptoms of which are experienced periodically. It is characterized by irritation and inflammation of the mucous membrane of the eyes, nose, and upper air passages, especially the nares, attended by profuse secretion, and in the advanced cases it is complicated by asthmatic attacks. Isolated cases may occur at any time of the year, but in this country the disease usually prevails from about the 20th of August until the latter part of September or until early frost, though similar affections are observed in May, June, and July, and occasionally even in winter. The attack usually occurs on nearly the same day of the month of each succeeding year, though in some seasons many individuals will be attacked several days before the expected time, and in other years the affection is correspondingly delayed by the temperature and atmospheric conditions.

In England hay fever generally occurs in June and July, and upon the Continent of Europe, where it is much less frequent, it also appears to occur considerably earlier than in this country. It is more frequently met with among men than women. It may occur at any age, but it is most frequent in middle life. I have seen it in children less than five years old and also in persons of advanced age. The disease is seldom found in persons belonging to the working classes, though exceptions to this rule are not very infrequent. Notwithstanding the greater prevalence of the exciting cause in the country, the disease is more frequent in cities than in rural localities. In this country it is comparatively infrequent south of the thirty-third parallel or north of the forty-seventh, and certain elevated regions are nearly or quite exempt from the disease, apparently because of the character of the vegetation and the low temperature.

Anatomical and Pathological Characteristics.

Hay fever is generally, though not always, attended by inflammation of the mucous membrane of the nose, eyes, and throat, and not infrequently this inflammation extends to the accessory nasal sinuses or even to the entire respiratory tract. The membrane is usually congested, reddened, and swollen, but exceptionally there is very little swelling, and not infrequently the parts are paler than normal.

Etiology.

Though the etiology of the affection is not fully understood, it is generally believed to result from a peculiar irritability of the nervous system, which in some persons is manifested by constitutional symptoms and in others by localized abnormal sensitiveness of a part or the whole of the mucous membrane of the respiratory tract. This abnormal sensibility renders the mucous membrane prone to inflammation which may be excited by various minute particles in the atmosphere.

Heredity and the neurotic diathesis undoubtedly predispose to this affection, and a great variety of agents may excite the attack. As first pointed out by William H. Daly, of Pittsburg, a hyperæsthetic condition of the nasal mucous membrane is one of the most important factors in the etiology of the disease; but the most common exciting cause of the attack is the pollen of *Ambrosia artemesiæfolia*, known also as Roman wormwood, ragweed, or hogweed, or that of *Solidago odora*, known commonly as golden rod. We find therefore, three essential factors in the production of this affection: first the neurotic habit; second, local hyperæsthesia; and third, the presence of irritating substances in the atmosphere. While the neurotic habit is frequently inherited, as shown by the occurrence of this affection in various members of the same family or in the offspring of those who have suffered from the disease, yet in the great majority of cases it appears to have been acquired. It has also been claimed, with some show of probability, that the disease is much more frequent in the lithæmic, a condition which probably causes many of the symptoms in the neurasthenic.

The neurotic influence in the production of the disease is well illustrated by the well-known incident related by Dr. John M. McKenzie, of Baltimore, in which an attack was brought on by the sight of an artificial rose. In the majority of cases it is easy to demonstrate a hyperæsthetic condition of some portion of the nasal mucous mem-

brane, but in exceptional instances this is not apparent. Though the pollen of the ragweed or of golden rod is the most common exciting cause of the affection in this country, that of certain grasses, as wheat, barley, oats, rye, and even Indian corn, may also excite the disease. There are also persons in whom this affection, like spasmodic asthma, may be brought on by exposure to dust, to the emanations of certain animals, or even to the bright rays of the sun.

I have known of one person who was unable to cross the street on a hot day in summer without sneezing violently unless he carried an umbrella. I have known of still another in whom attacks of sneezing were brought on frequently by exposure to a bright gaslight; though this person was not a hay-fever patient, the hyperæsthetic condition of the nasal mucous membrane was similar to that found in the majority of patients suffering from hay fever.

In regions comparatively free from the disease it is generally found that persons subject to the disease become worse in warm days or when the wind blows from the south, indicating that temperature, even though it is not sufficient to account for the origin of the affection in any case, has much to do with the symptoms. This aggravation of the disease by winds from certain directions is generally supposed to be due to their being laden with a greater amount of pollen, and doubtless this is in part correct, yet an experience with many cases has forced me to the conclusion that temperature alone is partly responsible.

Obstruction of the nasal cavities by swelling, exostosis, or nasal polypi is also said to be a cause of the disease, and I have seen a few patients in whom peculiarity in the digestive function at this time of the year would indicate to me a reflex origin. For example, one patient who was fond of tomatoes and watermelons and who could eat them with impunity at any other time of the year, was unable to do so during the hay-fever season without the most violent disturbance of the gastrointestinal tract.

Symptomatology.

The attacks often come on the same date of succeeding years, regardless of the temperature, the condition of the patient, or his environment; but a variation of a few days is not infrequent, apparently depending upon atmospheric changes, probably due in the majority of cases to the acceleration or delay in the growth of the plants that produce the pollen. It is probable that in some instances the regular recurrence of the attack upon the same day of the month and even at the same hour of the day is due to neurotic influences, but that this

is not so in the majority of cases is well attested by numerous facts, particularly those obtained from a study of the affection in young children.

There are two recognized types of the disease: the catarrhal and the asthmatic. In the former the disease usually comes on suddenly with irritation of the mucous membrane of the fauces, conjunctivæ, and nares, and is attended by frequent sneezing. In the latter variety the asthmatic features may be developed early or late, but commonly they do not occur until the latter part of the season, when the patient has already suffered for several weeks from nasal affections. The asthma in hay fever commonly differs from spasmodic asthma in the greater persistence of the dyspnœa and in the occurrence of the paroxysms quite as frequently in the daytime as at night.

In most cases the disease is ushered in by tickling or stinging sensations in the Schneiderian mucous membrane, accompanied by attacks of sneezing and itching of the conjunctivæ, with profuse lacrymation, or by burning and stinging sensations in the throat. In others the first symptoms are severe neuralgic pains in the eyes and back part of the head, or swelling of the conjunctivæ, eyelids, or tip of the nose. Constitutional effects are denoted by elevation of temperature, aching of the muscles, general malaise, and sometimes by great weakness. In many subjects there is no alteration of the pulse or temperature during the attack, but in others the pulse is increased in frequency ten or twenty beats or even more, and the temperature is raised two or three degrees. These latter symptoms are more likely to be observed when the patient has already suffered for several days from the attack. They are doubtless due, in many cases at least, to disturbed rest rather than to the disease itself. The congestion and swelling of the mucous membrane of the nose interfere seriously with nasal respiration and probably in many cases are the reflex cause of the spasmodic affection of the bronchial tubes.

Free lacrymation is a common symptom, and there is profuse watery secretion from the nose, which irritates the upper lip. After a few days this secretion becomes muco-purulent. The symptoms vary much from day to day and even at different times of the same day, according to the exposure of the patient or the direction of the wind. Many patients experience sharp stinging sensations in the roof of the mouth which become a source of great discomfort. The sneezing which usually ushers in the attack sometimes becomes a very distressing symptom. Usually during the first two or three years of the disease the patient does not suffer from asthma, but finally in most cases the asthmatic attacks make their appearance towards the latter part of the season, and subsequently are liable to come on ear-

lier with each succeeding year, until finally they may be coincident with the inception of the hay fever. Commonly with the cool fall weather the symptoms grow milder, and after two or three frosts they speedily disappear; but frequently the cough and catarrhal symptoms continue for two or three weeks after the disappearance of the exciting cause and in many instances several weeks or even months elapse before the patient regains his usual vigor.

Diagnosis.

Hay fever may be confounded with simple acute rhinitis or with spasmodic asthma. The essential points of difference are the history, the abrupt commencement, and the excessive nasal irritation, together with asthmatic symptoms which are apt to occur during the daytime instead of at night.

Simple acute rhinitis comes on more gradually with irritation and dryness of the nasal mucous membrane, followed after ten or twelve hours by a free thin serous discharge, succeeded in two or three days by a muco-purulent secretion, which subsides after a few days, so that in the majority of cases complete convalescence is established within a week or ten days. In hay fever we can usually obtain a history of previous attacks occurring at the same time of the year, which have lasted for five or six weeks, but if we see the patient in the first attack it is sometimes impossible to determine whether we have to deal with simple rhinitis or with hay fever. In such cases we must wait for further development, and sometimes it will not be possible to be sure of our diagnosis until another year comes around with its periodic attack. A detection of very sensitive areas of the nasal mucous membrane, particularly upon the posterior part of the septum or the posterior end of the inferior turbinated bodies, is of much value in differentiating cases, as these areas are much less common in simple acute rhinitis than in hay fever. In hay fever sneezing is a more prominent symptom than in acute rhinitis, and profuse lacrymation and swelling of the eyelids, not present in the latter, are important symptoms.

Spasmodic asthma is distinguished from hay fever by the history, and usually by the absence of nasal symptoms; but we must not overlook the fact that there are many cases of so-called spasmodic asthma, that lack the periodic regularity of hay fever and some of its essential symptoms, which are nevertheless undoubtedly produced by causes similar to those which excite the attacks of hay asthma.

Prognosis.

The attacks of hay fever usually continue with varying severity from four to six or eight weeks, according to the patient's surroundings and the atmospheric conditions. The asthmatic attacks may last from a few hours to two or three days, and may disappear as suddenly as they came. Some patients become more susceptible to the disease with advancing years and with others immunity from attacks is apparently acquired by avoiding the exciting cause for a few seasons. Those who escape the attack by a change of climate are generally much more comfortable if they leave home before the attack comes on, and it is probable that in many instances if this plan were followed up regularly for a few years the susceptibility would entirely disappear.

Under appropriate treatment many cases can be cured and many more greatly alleviated, but some are very little affected by any medical measures, though practically all can be relieved by appropriate climatic conditions.

Treatment.

In the treatment of the disease we must constantly keep in mind the three important factors in its production—viz., the irritating pollen or other substance in the atmosphere, the neurotic habit, and the hyperæsthetic local condition. In the great majority of cases the irritating substance in the atmosphere is an essential element, and therefore it has been found that the attack may commonly be prevented by a change of climate. Sometimes so slight a change as from city to country or *vice versa* is beneficial, but most patients find greatest relief in cool localities by the Northern lakes, in certain places near the sea shore, or in some high altitudes where the ragweed or golden rod are seldom found. A trip upon the lake or ocean, removing the patient from the pollen in the atmosphere, is equally efficacious. In order to secure the greatest comfort, the patient should leave home before the attack is expected, and should not return until after there have been two or three heavy frosts in the fall. The symptoms are likely to be greatly aggravated by the railway journey, and I have no doubt that the delay in leaving home or the irritation experienced on the journey often accounts for symptoms which persist in spite of removal to a good climate. In this country the most favored spots are in the White Mountains of New Hampshire, in the Adirondacks, and in the regions about Macinac, Petoskey, or Marquette, in the northern part of Michigan, or various places in north-

ern Wisconsin. There are, however, many other places where different individuals will escape the attacks, and no locality will be found equally beneficial for all persons, as some suffer severely where others get complete relief. Many persons escape the disease in the high altitudes of our Western States and Territories, and it is probable that the majority of persons would be free from the attacks in new countries where the growth of ragweed or golden rod is sparse. In many places along the country roads, but especially in cultivated fields that have been reaped, the ragweed springs up in great abundance, and by the latter part of August fills the atmosphere with its pollen; so that in seeking a place exempt from hay fever, one should select a locality where there are few roads or cultivated fields.

For the constitutional conditions predisposing to the attack, nerve tonics and sedatives are especially indicated, and should usually be commenced four or five weeks before the attack is expected. It is well also to continue them until convalescence is established; for this purpose various preparations of quinine, strychnine, arsenious acid, hyoscyamus, and asafœtida, or some of the preparations of valerian or camphor, are most serviceable. Though the bromides would seem indicated for the same purpose, they do not appear to have much, if any, influence in preventing the attacks. In those predisposed to rheumatism or gout, remedies appropriate for these diseases should also be administered, and the diet should be regulated to prevent accumulation of nitrogenous products in the blood. In those subject to indigestion the stomach and bowels should be carefully regulated previous to the time when the attack is expected.

Among the remedies which have seemed to me most beneficial in warding off the attacks are brucine phosphate, extract of hyoscyamus, valerianate of quinine, and camphor with or without sodium salicylate, salol, phenacetin, acetanilid, or asafœtida. These are not only advantageous in delaying or preventing the attack, but seem to be of much value in mitigating the patient's suffering during its progress.

If we fail to prevent the attack we must endeavor by symptomatic treatment to reduce the disagreeable symptoms to the minimum. There are several remedies that in some persons, at least for a time, will relieve the prominent symptoms of the disease, but they are not applicable to all patients alike; therefore we are obliged to try those that seem most likely to accomplish the results, and if we do not succeed with these, others should be substituted. In the early stages opium and belladonna in small doses are often of the greatest benefit for people who can take them without discomfort. For example, in suitable cases excellent results are obtained from five to eight drops

of the tincture of belladonna or the deodorized tincture of opium or both combined; or instead of these, from gr. $\frac{1}{12}$ to gr. $\frac{1}{8}$ of morphine or from gr. $\frac{1}{200}$ to gr. $\frac{1}{120}$ of atropine or both combined. Atropine or hyoscyamus in small doses is especially useful in checking the nasal secretion and in preventing the tendency to sneeze, but the after-effects of either, especially of atropine, are peculiarly disagreeable to many persons. Local stimulating inhalations of camphor, ammonia, iodine, or chloroform are sometimes useful, providing they are not used so strong as to increase the irritation.

Itching of the conjunctivæ is best relieved by weak solutions of the acetate of lead, as recommended by the late Sir Morell Mackenzie, or by a saturated solution of boric acid in camphor water. Some patients will be more relieved by a solution of from five to ten grains to the ounce of sodium biborate in camphor water. With one of these the eyes may be bathed as frequently as desired, and a few drops of the same solution may be placed within the lids every two or three hours. The rule should be that the preparation, whatever it is, should not be strong enough to cause smarting for more than two or three minutes, and that it should lessen rather than increase the congestion after a few hours. Great relief from the itching and smarting may sometimes be afforded by bathing the nose and eyes with either very hot or very cold water. The eyes may be protected to a considerable extent by large dark glasses, or by goggles in which the glass is set in a framework of fine wire.

The nasal mucous membrane may be protected from the irritating particles by wearing plugs of wool in the nostrils, or by a respirator that will perfectly filter the air; but most patients object to the wool because it causes such tickling as to become intolerable to many of them, and respirators are so seldom worn in this country that very few patients can be induced to adopt them. Irritation of the lips and nostrils by the secretions may be largely prevented by the application of some kind of ointment or vaseline. The most satisfactory ointment that I have used for this purpose is composed of six grains of carbolic acid, four minims of oil of roses, twenty-five grains of iodol, ten grains of the oxide of zinc, to four drachms of lanolin. Soothing sprays to the nasal cavities are very grateful to the patient and often mitigate greatly the severity of the attack. In those in whom for any reason oily applications are objectionable, a saturated solution of boric acid in distilled water may be tried. In other cases it would be better to make the solution with camphor water, and in still others it would be desirable to add minute quantities of atropine, morphine, or cocaine. The latter remedy should never be used in a strength of more than one per cent., less

than this being preferable in most instances. Cocaine in larger quantities gives prompt relief to many cases, at least for a time, but with protracted use its effects are lost, so that larger doses have to be employed, and its frequent use under such circumstances is often followed by the most serious consequences. It is never safe to order cocaine for a patient without writing across the face of the prescription that it must not be repeated without a special order, and it is very much better for the physician to supply the remedy himself, in order that he may be sure it is discontinued before harm results from its use. I have seen many patients greatly injured by the protracted use of this drug, and some whose whole lives have been wrecked by carelessness of the physician in giving them a prescription of which it formed a part. Oily sprays containing various substances are usually more beneficial than aqueous solutions, but occasionally oil, of whatever kind, appears to do more harm than good. In such cases aqueous solutions must be employed. An excellent nasal spray for hay fever during the season is composed of one-fourth of a grain of thymol, two minims of the oil of cloves, and three grains of the alkaloid cocaine to one ounce of pure liquid albolene; but when the patient is going to a distance, or if for any other reason it is necessary to give him a prescription that may be duplicated, even this small quantity of cocaine is not safe. The amount of the active ingredients in this prescription may be slightly increased if the nasal mucous membrane is not extremely sensitive, but ordinarily this is as strong as can be used without discomfort during the height of the attack. Care should always be taken that the application, whatever it may be, is not irritating. Sometimes it is well to add to the above prescription half a grain to one grain of menthol or half a grain of camphor. Such a spray should be used five or six times a day or as much oftener as desired. The most satisfactory instrument for this purpose is the Davidson atomizer No. 50, shown in Fig. 5.

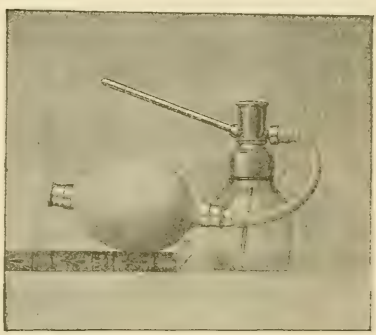

Fig. 5.—Davidson Atomizer No. 50 for Oil. One-quarter size.

A powder containing three or four per cent. of hydrochlorate of cocaine, with or without small quantities of atropine or morphine, is more convenient for application and will usually give the patient great comfort during the height of the attack, but it is especially important that no prescription be given for this powder, as it is very

liable to do much damage if long continued. In whatever way cocaine is employed the patient should not use more than one-third of a grain daily, and this should not be long continued. The powder that has proven most beneficial in such cases in my hands contains from three to four per cent. of the hydrochlorate of cocaine, one and one-half per cent. of the bicarbonate of sodium, one and one-half per cent. of the biborate of sodium, three per cent. of the light carbonate of magnesium, and enough sugar of milk to complete the quantity. When the nasal cavities are sore, or when there is much secretion, it is often advantageous to add to this powder from one-half to one per cent. of alumnol and fifteen to twenty-five per cent. of iodol. The powder is most conveniently applied with a small glass tube about four inches in length, with an eighth of an inch calibre, one end of which has been flattened, the other being attached to a rubber tube about ten inches long (Fig. 6). The latter being removed, the

Fig. 6.—Insufflator. One-third size.

powder is worked into the round end of the glass tube until it is filled up to the extent of from a quarter to a half inch, when the rubber tube is again passed over it. The patient then places the flattened end of the tube in the nostril, and taking the other end of the rubber tube between the lips gives a quick puff and blows the powder thoroughly into the nasal cavity.

During an attack of hay fever nasal douches of weak solutions of quinine, salicylic acid, sulphuric acid, or other antiseptics have been recommended on the theory that they would destroy microbes that set up the irritation. It is well known that the essential cause of the irritation is the pollen of certain plants, as already indicated, and it is doubtful whether these antiseptics have any beneficial effect upon the disease, except that they wash out the irritant; but it is certain that douches of warm water containing salines or other substances sufficient to obviate the irritation that would result from water alone, are sometimes beneficial. Some persons believe that they have obtained great relief from some of the various washes suggested, and there can be no objection to trying any one of them, providing the solution is made weak in the beginning and gradually increased in strength until its effects are determined.

It has been stated that this disease is sometimes due to the rheumatic or gouty diathesis, and upon this hypothesis salicylate of sodium, citrate of lithium, and other remedies have been highly rec-

ommended, but a physician cannot try any of them long without losing all confidence in them. Nevertheless in persons predisposed to rheumatism or gout, these remedies may be helpful in warding off an attack of hay fever or relieving it, just as they might be in warding off or relieving an attack of sciatica, and it certainly behooves the physician to search for, and if possible, remove every complicating condition.

I have obtained most relief by the internal use of nerve tonics and sedatives, such as brucine phosphate, hyoscyamus, valerianate of quinine, and asafœtida, using, however, salol or the antirheumatic remedies where they seem to be indicated. For relieving the fever which not infrequently attends the attack, acetanilid, phenacetin, or antipyrin may be employed in small doses. The asthmatic complications are best relieved by the same remedies that are useful in spasmodic asthma, yet they also often fail to meet our expectations. In persons in whom there is no idiosyncrasy contraindicating the use of opium, I commonly prescribe for the asthmatic attack half a grain of codeine, ten grains of bromide of potassium, and ten grains of chloral in two drachms of the syrup of grindelia robusta, to be repeated in half an hour or an hour unless relief is sooner obtained. The other internal remedies recommended for asthma and the various fumigations that often relieve the spasmodic affection may also be tried in the asthmatic attacks of hay fever, but usually they have but little effect. The irritable condition of the nasal mucous membrane and the unpleasant symptoms caused by its swelling during the attack may be relieved in a large number of cases by a judicious cauterization. Dr. John O. Roe, of Rochester, thinks that a very large percentage of cases may be thus relieved or entirely cured. Dr. Charles Sajous, now of Paris, some years ago stated at one of the meetings of the American Laryngological Association that about forty-five per cent. could be thus cured, and about twenty-five per cent. greatly relieved, but the remainder were not materially benefited. These statements appear to correspond closely with my own experience, though out of a large number of cases that have been under my care, in comparatively few have I been able to follow the treatment to a successful issue, for the reason that many patients have come to me just as the hay-fever season was approaching, so that there was not time to complete the work before the attack, and after the season was over they have not cared for treatment. Those who came during the height of the disease were not cauterized, as I believe in the great majority of cases such treatment would be worse than useless. There are certainly a good many—and I believe the percentage is not far from that stated by Sajous—who may be greatly

benefited or cured by proper cauterizations, the removal of polypi or obstructing spurs from the septum, or the reduction of hypertrophies of the turbinated bodies.

In practically all cases of hay fever an examination of the nasal mucous membrane by the probe will reveal one or more hypersensitive spots, which are most apt to be located at the upper and back part of the septum and posterior ends of the inferior turbinated bodies. The hypersensitiveness is also common on the anterior portion of the inferior turbinated, and it is not very infrequent on the middle turbinated bodies. In severe cases it may extend over the greater portion of the nasal mucous membrane. In many cases swelling of the inferior or middle turbinated bodies is also observed, but it may not be present during the intervals, though it is usually present at some time during the attack. In a considerable number of these patients spurs from the septum are noticed, but they are seldom if ever the cause of the hay fever; indeed, in the majority it is doubtful whether these spurs have anything to do with the irritability of the mucous membrane, for it has been demonstrated that out of a hundred supposedly healthy persons about fifty per cent. will have such spurs from the septum. However, there are some cases in which a spur stands out prominently and sharply so as to impinge against the mucous membrane of the opposite side of the nasal cavity, particularly when it is swollen, and in these it is generally found necessary to remove the spur before much relief can be obtained. I would therefore recommend that permanent obstructions in the nasal cavity be removed, that hypertrophies or even swellings of the turbinated bodies be reduced, and that hypersensitive spots be superficially cauterized.

Spurs may be removed with the cautery, trephine, saw, or chisel, according to the judgment and skill of the operator. Hypertrophied

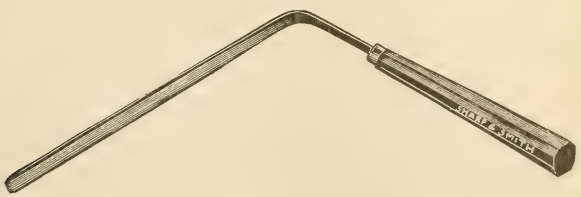

Fig. 7.—Aluminium Applicator. One-half size.

turbinated tissue may be removed by the snare or scissors when extensive, but when moderate or when the tissues are simply swollen, it is best to reduce the obstructing mass by linear cauterizations, which to my mind answer a much better purpose than small cauterizations here and there with a galvano-cautery point. I am also strongly in favor of the galvano-cautery in preference to chromic acid

or other caustics, though there is no doubt that these latter may be used effectively in some cases. I am satisfied that the pain and discomfort caused the patient are usually much greater with chemical caustics than with the galvano-cautery, and the results have not seemd to me so thorough. If mucous polypi are present, they must be removed by means of the snare or cautery or otherwise as may seem best to the operator. Before attempting any of these operations the parts should be thoroughly anæsthetized with cocaine, which is best applied by means of a thin cotton swab wound upon a flat aluminium probe as shown in Fig. 7.

The solution of cocaine that I prefer, because of its speedy action and the comparative absence of constitutional effects, is the following:

℞ Atropinæ,	. . . . .	gr. $\frac{1}{10}$
Strophanthini,	. . . . .	gr. $\frac{1}{5}$
Cocainæ hydrochloratis,	. . . . .	gr. xx.
Acidi carbolici,	. . . . .	gr. v.
Olei caryophylli,	. . . . .	♏ v.
Aquæ,	. . . . . q. s. ad	℥ i.

Misce et sig. Use locally.

In producing local anæsthesia this solution is thoroughly rubbed over the parts with a thin swab of cotton, the patient is then allowed to wait for a minute or a minute and a half, when the application is repeated. From two to five applications are usually sufficient, but in those who have been using cocaine to relieve the hay fever or in those in whom the parts are peculiarly sensitive, ten or a dozen applications may be necessary; and now and then a case is met with where a ten-per-cent. solution of cocaine must be applied before anæsthesia can be secured. I have occasionally found it necessary to have a patient discontinue the use of cocaine and wait a few weeks before commencing treatment in order to secure sufficient anæsthesia from the drug.

When the turbinated bodies are swollen or moderately hypertrophied they may be most satisfactorily reduced by deep linear cauterizations made with the electrode shown in Fig. 8.

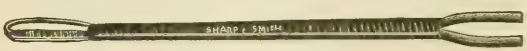

Fig. 8.—Knife Electrode. Half size. Platinum blade of No. 21 wire.

This instrument is five inches long, and the platinum knife at its distal end is five-eighths of an inch in length and consists of a No. 21 platinum wire soldered into the copper stems.

In making the linear cauterizations, after the parts have been thoroughly anæsthetized, this is passed through the naris to the back

end of the body to be cauterized. The patient is then told to hold his breath in order to escape the disagreeable taste of the smoke, the platinum wire or knife is pressed against the tissues, the electric current is turned on sufficiently to heat the wire to a white heat in a second and a half; it is then drawn slowly forwards, sometimes being moved back and forth until the soft tissues are burned through and the bone is slightly touched in two or three places along the course of the burn. Commonly I make the linear cauterizations from the back entirely to the front end of the turbinated at one time. A similar cauterization may be made upon the opposite side of the nose at the end of two or three weeks, but not sooner; thus two or three cau-

FIG. 9.—Guarded Electrode. One-half size. Platinum end of No. 21 wire, guard of vulcanized fibre.

terizations may be made on each side, seldom more than two being required for the swelling or hypertrophy of the turbinals. The superficial cauterizations are made by means of a flat guarded electrode, as shown in Fig. 9.

This electrode is about five inches in length and has a point of number No. 21 platinum wire which is guarded upon one side by vulcanized fibre so as to prevent burning the opposite side of the naris. The superficial cauterizations are not intended to destroy tissue, but to act more as a blister would upon the skin. Indeed, after they have been made no scar should be left. In performing the operation, after anæsthesia has been secured, the naris should be sprayed with liquid albolene. The flat electrode is then introduced, and when heated is rubbed quickly over the spot to be cauterized until the mucous membrane is thoroughly whitened, having much the appearance it would have if touched by the solid nitrate of silver. It is seldom wise to cauterize a spot more than half an inch in diameter, though occasionally patients will tolerate more, and in very sensitive patients it is better to do even less. Cauterizations of this kind may be repeated more frequently than the deep linear burns above referred to. I have sometimes made these operations on a patient as often as three times a week, but this is too often for the comfort of the patient, and such frequency cannot be recommended excepting in rare cases peculiarly conditioned; even then they ought not to be made oftener than once in five or six days, and when thus close together they should be alternately in the opposite nasal cavities, so that the reaction caused by the cauterization may not light up inflammation again in the parts affected by the one that preceded it. Cauterizations like that just described should be carried out over all of the sensitive mucous mem-

brane in the nasal cavities, and occasionally they will have to be repeated once or twice in the most sensitive spots, because the burn is not always deep enough at first. Notwithstanding this it is better to make the burns too superficial than too deep, because it would be a great misfortune to the patient to have the mucous membrane destroyed and replaced by cicatricial tissue, a result that not infrequently follows the work of novices. After nasal cauterizations, we may give the patient some cotton wool to wear in the nostril of that side for four or five days to prevent taking cold, the direction being that he wear it whenever out of doors but not when in the house, unless he so desires. We should also give the patient a spray containing a third of a grain of thymol with three minims of the oil of cloves to the ounce of liquid albolene, which he is directed to spray freely into both nasal cavities three or four or more times a day during the entire treatment. The patient should have a certain amount of the cocaine powder already mentioned, of which he is directed to throw a small quantity into the nose two or three times a day, if it becomes obstructed, for the purpose of keeping down the swelling. About four days later, in cases of the linear cauterizations, this powder is modified by adding twenty-five per cent. of iodol, and the patient is directed to use it only once or twice a day; this latter powder is sometimes given immediately after superficial cauterization instead of that first recommended.

By this method we may get rid of the hypersensitiveness of the nasal mucous membrane and may cure, or at least relieve, very many of the symptoms of hay fever. Cauterizations should cease as soon as all of the sensitive membrane has been treated. Meddlesome surgery is quite as much to be deprecated in the nose as in any other part of the body, and we should never forget that it is much better to do too little than too much. As soon as all the sensitive surface appears to have been reached, the patient is told to use the spray already recommended three or four times a day for a few months in order that the parts may perfectly heal, and we may determine whether more cauterization is necessary. It frequently happens that the following year, or sometimes two years later, it will be found necessary to cauterize a few other spots, or perhaps some of the same spots first cauterized, in order to accomplish the desired results. In mild cases ten or twelve cauterizations are sufficient, but in the more severe twenty or thirty or even more may be needed to cure the whole Schneiderian membrane of its hypersensitiveness. The treatment is best carried out during the warmer portions of the year, that is in the spring preceding the attack of hay fever or in the fall after it has disappeared, and it is

best to proceed slowly in order to give the patient as little discomfort as possible. There is no need of continuous treatment in such cases, and we can see no excuse for the daily attendance of the patient at the physician's office. Between the superficial cauterizations nothing whatever is likely to be needed by the patient excepting what he may himself accomplish by means of the spray and powder already referred to.

Although cauterizations during the height of the attack of hay fever have occasionally been followed by beneficial results, the practice cannot be advised, because it is likely to do more harm than good; therefore during the attack we recommend symptomatic treatment only, to give the patient as much comfort as possible. Preceding the attack we attempt to prevent it, and in the intervals we endeavor by proper cauterizations to remove its cause, provided this is located in the nasal cavities. When asthma has already developed we cannot expect as much from cauterization as in cases where the symptoms are still chiefly nasal, though even in the former the most satisfactory results are sometimes obtained. This will be shown in one of the following cases that are here reported merely to illustrate what may be accomplished in typical cases of hay fever by cauterizations of the hypersensitive nasal mucous membrane.

Case I.—The following illustrates the good results that may sometimes attend simple tentative treatment. The patient, M. G., aged 8 years, was brought to me in May, 1892, complaining of frequent sneezing caused by dust and other irritants and well-marked symptoms of hay fever during the fall for the last three or four years. The diagrams 10, 11, 12, and 13 show the areas that were hypersensitive at the beginning of treatment. In this case, owing to the child's age, her distance from home, and her inability to remain in the city, it was deemed best to try tentative treatment. She was therefore given an oily spray containing four minims of the oil of cloves to the ounce of liquid albolene; this she used freely for a short time, and afterwards used liquid albolene alone continuously whenever she was subject to sneezing spells and during the hay-fever season, with the results of completely overcoming the disease in about two years.

Case II.—Mrs. E. S., aged 48, has had hay fever every summer for eighteen years, beginning about the 1st of September, and for the last three years has had asthma, not confined to the hay-fever season. The hay fever in this patient is usually ushered in by symptoms of gastric and intestinal indigestion produced by various foods, and it is an interesting fact that with her green corn or watermelon will give great distress at this season, though at other times she enjoys them very much and they are eaten with impunity. This patient first came under my care in April, 1893. She had previously been a very healthy woman excepting for the hay fever and slight attacks of rheumatism and the asthmatic attacks already referred to. During

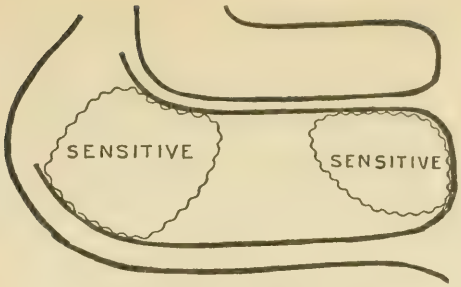

FIG. 10.—Right Turbinated Bodies.

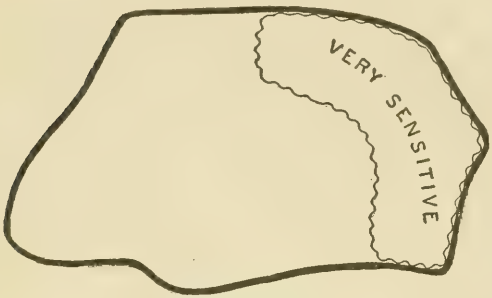

FIG. 11.—Right Side of Septum.

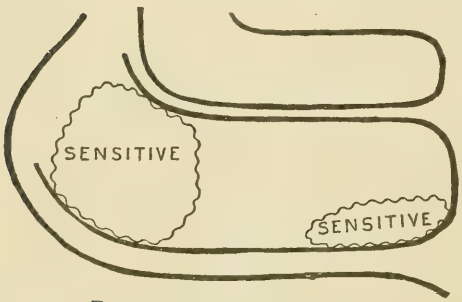

FIG. 12.—Left Turbinated Bodies.

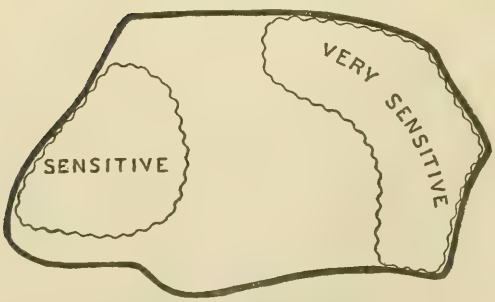

FIG. 13.—Left Side of Septum.

CASE I.—FIGS. 10-13.—Diagrams Showing Sensitive Areas at the Beginning of Treatment. No cauterizations made. The wavy lines indicate the boundaries of the sensitive areas.

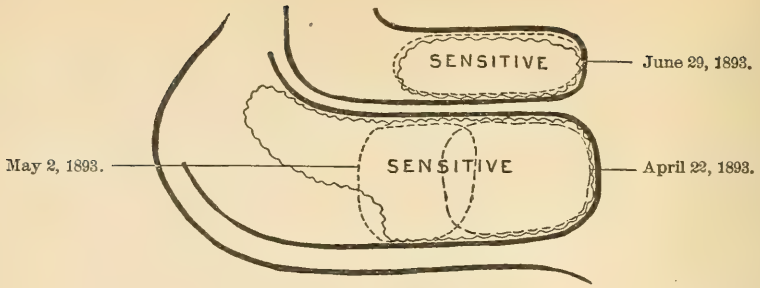

Fig. 14.—Right Turbinated Bodies.

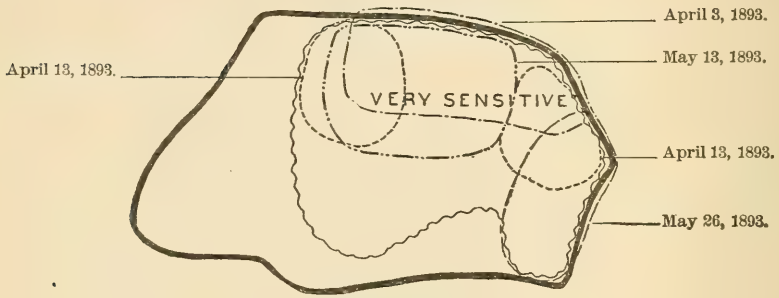

Fig. 15.—Right Side of Septum.

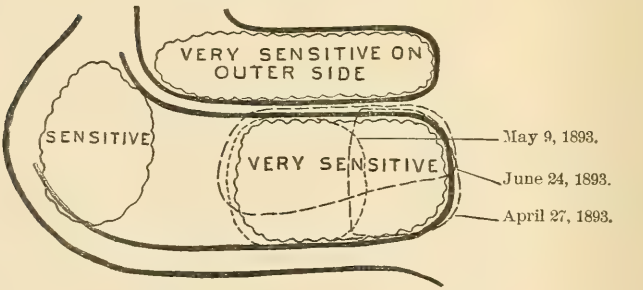

Fig. 16.—Left Turbinated Bodies.

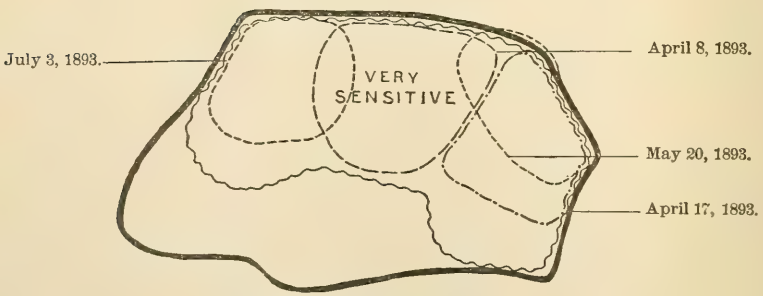

Fig. 17.—Left Side of Septum.

Case II.—Figs. 14–17.—Diagrams Showing Original Sensitive Areas and Early Cauterizations. The wavy lines represent the boundaries of the sensitive areas; the dotted lines limits of the superficial cauterizations. The dates are those of the several cauterizations.

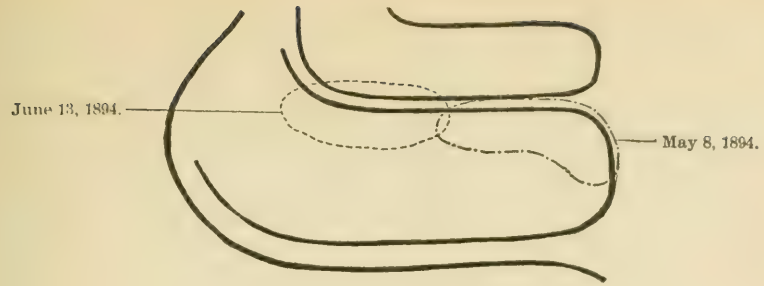

Fig. 18.—Right Turbinated Bodies.

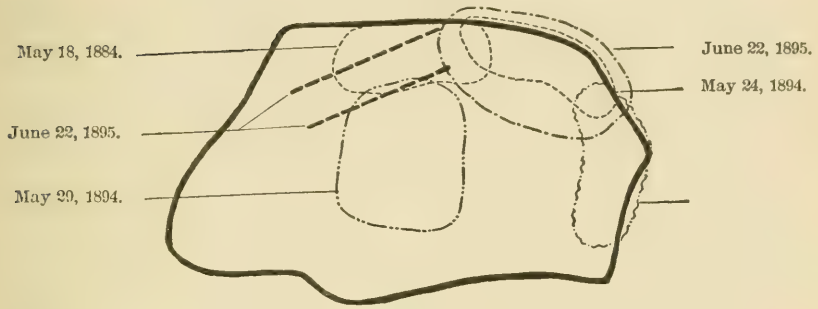

Fig. 19.—Right Side of Septum.

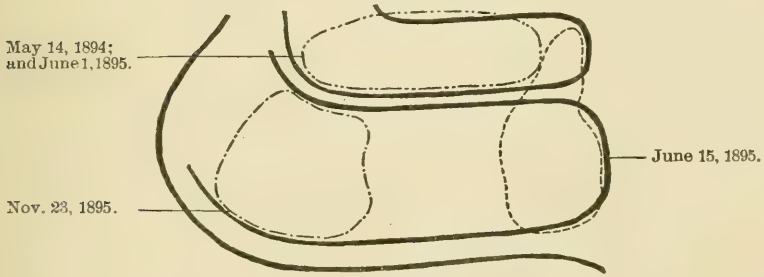

Fig. 20.—Left Turbinated Bodies.

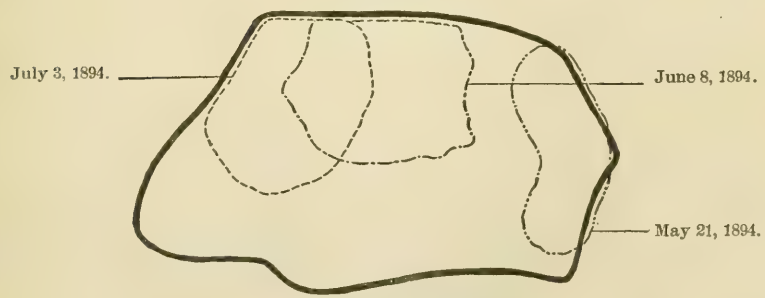

Fig. 21.—Left Side of Septum.

Case II.—Figs. 18-21.—Diagrams Showing Late Cauterizations, Some of Them Extending Over the Areas Formerly Cauterized. Thirty operations in all. The heavy lines in Fig. 15 represent the site of deep linear cauterizations. The dates are those of the several cauterizations.

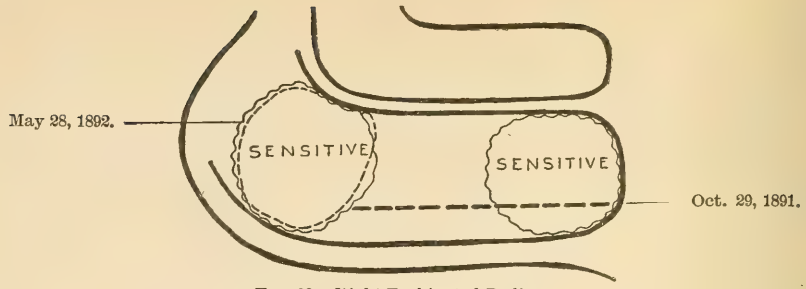

FIG. 22.—Right Turbinated Bodies.

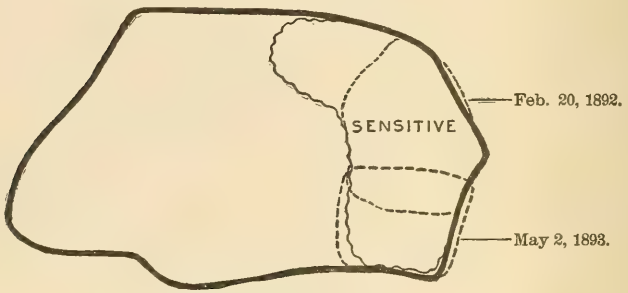

FIG. 23.—Right Side of Septum.

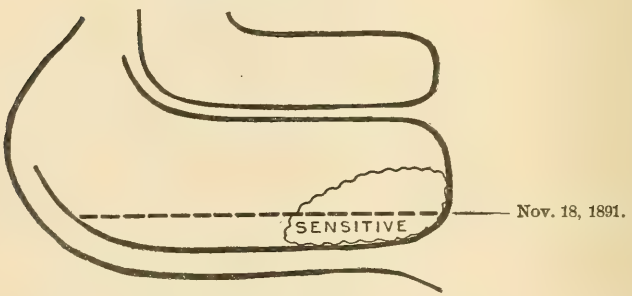

FIG. 24.—Left Turbinated Bodies.

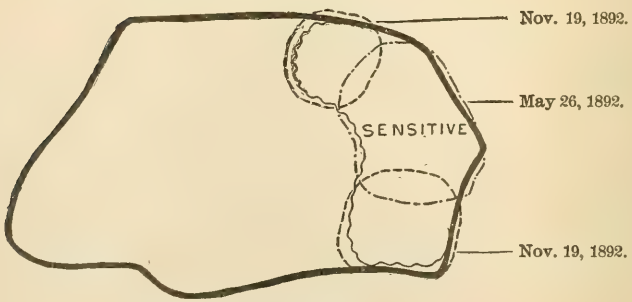

FIG. 25.—Left Side of Septum.

CASE III.—FIGS. 22–25.—Diagrams Showing Original Sensitive Areas and Areas Cauterized. The dates are those of the several operations. The wavy lines represent the boundaries of the sensitive areas; the light broken lines mark the limits of the superficially cauterized areas; the heavy lines indicate deep linear cauterizations.

her treatment various remedies already recommended were employed from time to time. During the spring and summer of 1893 the sensitive areas of the nasal mucous membrane were cauterized, as shown in the diagrams 14, 15, 16, and 17.

During that autumn, though she remained in Chicago subject to all of the influences of hay fever, she escaped the attack for the first time in eighteen years; but later she had a few slight attacks of asthma. The following year it was found necessary to cauterize a few more spots and she again escaped the hay fever, although she was subjected to all the influences that had commonly produced it. In June, 1895, it was noted that there were no sensitive places in the left nasal cavity, but some small spots were found in the right side and a few more cauterizations were made. She was away for a couple of weeks during the summer of 1895, but suffered none from the nasal symptoms of hay fever, either before she went away, while she was gone, or after her return, though she came back the 27th of August. She had three or four slight attacks of asthma during the months of September, October, and November; they were in no instance severe. Although the good results in this case are in part due to the remedies employed, the prevention of the attacks of hay fever must be largely attributed to the cauterizations. At present I find no hypersensitive areas in the nasal chambers. The diagrams 18, 19, 20, and 21 show the cauterizations that were made in 1894 and 1895, very few of them being made in the latter year.

Case III.—Mr. T. F. J., aged 43, came to me in October, 1891, suffering from cough which had been present for three months, and asthma that had troubled him more or less for several years. He complained of a good deal of obstruction in the nose and excessive secretion with crackling sounds in the ears. He had been subject to severe attacks of hay fever for several years. His general health was good; he had never had rheumatism or suffered from other illness excepting the diseases of childhood, but was troubled somewhat with indigestion. There were no abnormal signs over the lungs or heart.

The nasal cavities were about two-thirds closed by swelling of the turbinated bodies, the pharynx was relaxed and sensitive, the tonsils slightly enlarged, the larynx normal. Upon examination with a flat probe large sensitive areas were discovered in the nasal cavities upon both sides and it was demonstrated that the partial closure of these cavities was due to swelling of the soft tissues. Cauterizations were made at intervals during 1891, 1892, and 1893, as shown by the diagrams 22, 23, 24, and 25.

During the fall of 1892 he had considerable hay fever, though less than in the previous years, but the asthma was very annoying. During 1893 the cauterizations were completed and I saw nothing more of the patient until November, 1895, when he told me that he had been practically free from hay fever for the last two years and had had very little asthma, but the paroxysms were again returning. At this time the nasal mucous membrane was found to be normal. During the last two years he had been exposed to the same conditions as formerly and had taken very little precaution to prevent the hay fever, so that the relief must be attributed to the cauterizations.

DISEASES OF THE MEDIASTINUM.

BY

E. MAIN,

PARIS.

DISEASES OF THE MEDIASTINUM.

The diseases of the mediastinum form one of the shortest chapters in pathology. Indeed, they are relatively of infrequent occurrence; and, as an accurate diagnosis of their nature is almost always difficult, and successful treatment of them is exceedingly rare, it is not surprising that their description is circumscribed to very narrow limits. The mediastinal region, however, by reason of the important organs wholly or in part contained in it, presents a most interesting field for anatomical study; and the disorders, primary or secondary, of these organs constitute the entire pathology of the mediastinum and furnish also its general symptomatology.

By the term mediastinum is understood a cavity comprised within the thorax, between the sternum in front, the spinal column behind, and the internal surface of the lungs on either side. The root of the lung forms a sort of pivot serving as a dividing point between two secondary regions which early writers chose to describe separately as anterior mediastinum and posterior mediastinum, the former comprised between the sternum and the root of the lungs, the latter between the root of the lungs and the vertebral column. Such an absolute distinction is now rejected by anatomists, who admit but one mediastinum, although still, for convenience of description, dividing it into two parts, anterior and posterior.

Without entering into further anatomical details foreign to our province, we shall simply enumerate the important organs found in this region; these are the thymus, the heart and pericardium, the arch of the aorta and the cardiac plexus, the innominate artery and vein, the superior vena cava, the common carotid and subclavian arteries, the pneumogastric, recurrent, and phrenic nerves, the trachea, the bronchiæ, the pulmonary arteries and veins, the thoracic aorta, the œsophagus, the large azygos vein, the small azygos vein, the thoracic duct, and the ramifications of the sympathetic nerve. All these different organs are enclosed in a mass of cellular tissue, in the midst of which are found also numerous lymphatic ganglia of varying size. These ganglia serve as the points of convergence for all the lymphatic vessels of the neighboring organs, and receive also

those from the lungs, bronchiæ, trachea, pericardium, and heart, as well as those proceeding from the walls of the thoracic cage. We shall not dwell upon the arrangement of these ganglia, of which certain authors distinguish a number of leading groups, but there is one particular to which we wish to direct attention, namely, the very great importance they bear in relation to pathology, and the part they invariably play in all diseases of the mediastinal region. Indeed, one might almost say that every affection essentially of the mediastinum is an affection of these ganglia.

From the foregoing enumeration of the parts found in this region, it might be inferred that the diseases of those different organs pertain to the pathology of the mediastinum. This, however, is not the case, for the description of those diseases will be found in other parts of this work. We need refer here only to aneurysm of the aorta and cancer of the œsophagus, which affections by their location form a part of the pathology of the mediastinum, but which are studied elsewhere. This elimination being made, there remain for us to deal with here only tumors arising from the lymphatic ganglia and abscesses.

Tumors.

Before considering in detail the various tumors, their nature and etiology, it would seem well to present at this point a comprehensive view of the general symptomatology of these diseases of the mediastinum. Whatever be the histological character of a particular growth owing to the relations and functions of neighboring important organs, there is almost always observable a certain identity of type which may be described here. This description embodies all that is most valuable in the study of mediastinal diseases; for, although it is quite often impossible to determine with precision the nature of the affection, it is for the most part practicable to diagnose the region affected.

Symptoms.

When, upon viewing a patient, the attention is attracted in the direction of the mediastinum, the first thing to do it is to uncover the thorax completely and examine it carefully. In this way a more or less marked irregularity of form may often be observed over the sternal region. Indeed, mediastinal tumors, whichever be the organ from which they take their origin, have a tendency, on attaining a certain bulk, to push the sternum outwards, particularly its lower extremity, and thus the eye may detect a slight abnormal convexity or

elevation of the surface. This sign may in like manner be discerned around the sterno-clavicular articulations. We shall mention only incidentally the pulsations which the observer may perceive in this region when there has been waste of the osseous tissue, as in cases of aneurysm of the aorta. As has already been remarked, it is in connection with this disease that these special symptoms should be described. Palpation of the region may reveal, in the supraclavicular hollow, the presence of ganglia of varying size, whose nature and consistence may possibly afford an idea of those included in the mediastinal cavity. Inspection and palpation of the affected region should of course be followed up by percussion and auscultation, as valuable diagnostic aids. Percussion reveals a dull area, where normally resonance should be elicited, varying in extent with the volume of the tumors, the percussion note elsewhere in the thorax being in general observed to be normal. Auscultation discloses a variety of symptoms—bronchitis, emphysema, and fine râles—indicative of congestion of the pulmonary tissue.

But a circumstance of peculiar interest, in cases of this order, and which we shall have occasion to mention again by and by, is the frequent existence of compression of a bronchus by the tumor. It is mostly on the left side that this compression occurs, and, consequently, that the following symptom is observed: Auscultation shows the patient's breathing to be normal, or nearly so, on the right side, but on passing to the left side one is astonished at the almost total absence of sound. The vesicular murmur has either disappeared altogether or undergone marked diminution; and one's first thought is of pleuritic effusion, but percussion shows an absence of flatness. We have, therefore, a lung into which the air either does not penetrate at all or penetrates imperfectly, owing to compression of the principal bronchus.

Auscultation of the heart may also furnish valuable signs. The bruits are often weak, the action is slow, and frequently there is a murmur which may erroneously be taken for a symptom of cardiac or vascular disease. The difficulty is certainly very great in certain cases, and frequent auscultation of the patient, in different positions, alternately lying and standing, as suggested by Potain, becomes necessary. Again, the murmur presents at times different degrees of intensity, and has even been known to disappear in advanced stages of the disease, an indication that no cardiac lesion existed, but merely compression of some large blood-vessel.

Side by side with these first symptoms there are others, no less important, which are also occasioned by the mechanical embarrass-

ment and the compression produced by the mediastinal tumor. These phenomena affect the trachea and bronchial tubes, and both the vascular and nervous systems.

Concerning the trachea, we have seen how much may be learned from auscultation when compression exists. Let us now recall the diminished intensity of the vesicular murmur, coexistent with normal percussion sound. We may at times observe the presence of *cornage*, that is to say, a wheezing sound heard during inspiration, and produced by the air passing through a narrowed passage; and, lately, attention has been directed to the phenomeonn called *tirage*, produced by the depression of the upper part of the sternum during inspiration, and also due to the tracheobronchial compression. This phenomenon occurs only in cases of very great oppression and when the bronchus is almost totally occluded. The dyspnœa is usually of nervous origin, although in certain cases the difficulty in respiration seems to be due to direct compression of the pulmonary tissue, since the intensity of the symptom varies with the posture of the patient. When the latter stoops forward, for instance, the dyspnœa will subside, as if in that position the tumor causing the obstruction left its pulmonary cushion temporarily to bear against the posterior surface of the sternum.

In the circulatory system we have to point out some noticeable signs which are often among the first to arrest the observer's attention. It is easily understood that the compression caused by a mediastinal tumor will determine in the vessels so interfered with blood stasis, accompanied by dilatation of the vessels themselves, congestion, and œdema, the symptoms possibly varying with the intensity of the pressure in the different vessels. If the pressure bears upon the arterial system—the truncus brachiocephalicus or the subclavian artery, for instance—the radial pulse may be found considerably weakened on one side, as may be seen by comparing it with the pulsations on the two sides. But in general there is nothing more striking than the signs of venous compression, though they do not occur in all cases. The patient may exhibit dilatation of the veins—jugular, subcutaneous, etc.—and, if the collateral circulation be sluggish, cyanosis and œdema. The eyes are red and injected, the lips purple, and the face more or less livid. When œdema exists the symptom is observed in the face, hands, and thorax, sometimes on both sides, though often circumscribed to one side only. Of œdema of the lower members but a few cases are to be found on record in the literature of diseases of the mediastinum. Consequent upon this passive congestion, the patients complain of headache, dizziness, and frequent bleeding from the nose. Thus we see that com-

pression of the blood-vessels plays an important part in the symptomatology of mediastinal tumors.

The nervous system, too, furnishes signs of great value, arising from structural changes of the important nerves of the region, namely, the pneumogastric, recurrent laryngeal, phrenic, and great sympathetic. Hence the cough commonly observed—a peculiar cough of nervous origin, the pertussis-like (*coqueluchoïde*) cough which Guéneau de Mussy regarded as characteristic of tracheobronchial adenopathy.

Dyspnœa and oppression are also symptoms of frequent occurrence. This dyspnœa may assume one of two different aspects: it may be either continual and of uniform intensity, or susceptible of exacerbation under the influence of certain causes, as, for instance, a particular movement or change of position. Genuine, characteristic paroxysms of asthma are not unusual, and attacks of angina pectoris, with all their attendant symptoms, are sometimes observed.

Should the nerves of the larynx be affected—and they always are in a greater or less degree—the patients suffer from hoarseness, aphonia, and spasm of the glottis. The lesions of the recurrent nerve give rise to paralysis of the cord determining the vocal troubles. But laryngoscopic examination is of great utility in these cases, as enabling an accurate diagnosis of paralysis of the vocal cord to be made. Lastly, cases have been observed of pupillary inequality which must certainly be due to lesions of the grand sympathetic.

If to the foregoing list we add difficulty of deglutition, due to compression of the œsophagus, we shall have completed the review of the general symptomatology of mediastinal tumors.

Are we, then, to infer that every patient on coming under observation presents all these symptoms simultaneously? Unfortunately not. Indeed, the diagnosis of mediastinal tumors is very often extremely difficult and embarrassing, particularly at the outset. The patient commonly complains of ill-defined pains in the chest, quite sharp at times, between the shoulders; at other times twinges of simple neuralgia of the diaphragm are felt, and frequently the physician has, in the beginning, no other symptoms of a more decided character to guide him.

Careful percussion and auscultation should never be neglected, what has been said heretofore in this connection being borne in mind.

The value of the cough as a symptom can scarcely be overestimated. When consulted by a person affected with an obstinate, paroxysmal cough—*toux coqueluchoïde*—one should always suspect a mediastinal affection of some kind, and in most instances the diagnosis will be confirmed by the appearance of fresh signs of compression.

Pathological Anatomy.

Having now considered the signs by which mediastinal tumors may be recognized, we may next inquire into the nature of those tumors, and that rather with a view to their pathological anatomy than as a means of diagnostic precision. For, granting that, in observing signs of compression in the mediastinal cavity, it is easy in some instances to refer that compression to the development of a neoplasm, traces of which exist already in the organism, it is far from being always so, and the physician is often greatly embarrassed how to pronounce upon the anatomical structure of the abnormally developed tissue. Tumors of every description may have their seat in the mediastinum, but many are discovered only on the post-mortem table. Thus we find mention of echinococcus cysts, melicerous and steatomatous tumors, etc. But it may be said that the three common affections of this order are: (1) Cancerous tumors, (2) tuberculous adenopathies, and (3) simple adenopathies. Cancerous tumors are, in the opinion of all who have examined into this question, those most frequently met with.

In many cases mediastinal *cancer* is the product of neighboring cancerous lesions, and it occurs generally in the sarcomatous or carcinomatous form. But there exists a primary form of cancer of the ganglia of the mediastinum, the more important since it affects young and apparently healthy persons; this form is lymphadenoma or lymphosarcoma.

When cancer, whether primary or secondary, affects the lymphatic glands of the mediastinum, it develops with great rapidity, invades all the surrounding organs, and becomes generalized in an amazingly short space of time.

Next after the cancerous tumors, in order of frequency, come the *tuberculous adenopathies.* The bacillus tuberculosis behaves in the ganglia of the mediastinum as elsewhere, having the same modifications and causing the same lesions, and the observer finds himself in the presence of fatty and of caseous degeneration. In some patients the ganglionic lesion constitutes the dominant feature, and for this reason a number of authors have devoted a separate chapter to this affection, under the name of ganglionic phthisis. This form of tuberculosis occurs at all ages. At the outset, the diagnosis may remain for some time in doubt. I have in mind the case of a woman in whom the final diagnosis was delayed until comparatively late. This patient was a woman, aged sixty-two, affected with dilatation of the stomach and intestinal atony, and in whose history could be found

nothing suggestive of tuberculosis. Although she had consulted me on several occasions concerning her gastro-intestinal affection, my attention had never been attracted to her lungs. One day she complained of an obstinate, dry, paroxysmal cough, of a character somewhat resembling whooping-cough. Careful percussion and auscultation elicited no sign pointing to modification of the respiratory murmurs, nor could I find anywhere any trace of glandular engorgement. I prescribed antispasmodics, in conjunction with arsenic and tonics. When I next saw the patient, after a lapse of six or eight months, she was much reduced in flesh, and complained of evening fever and night sweats. Percussion revealed an area of dulness on the right side, and on auscultation there was heard a short, puffing respiration, with prolonged expiration on the same side. The cough meanwhile persisted, and with the same character as before. A diagnosis of tuberculosis was then imperative, with probable participation of the tracheobronchial glands, as indicated by the cough. Some months later the patient became affected with general tuberculous adenitis, most marked in the glands of the neck. This form, however, proceeds slowly; and as I write these lines the patient still lives in tolerable immunity from suffering, in the third year after the first appearance of the pulmonary symptoms.

Side by side with tuberculous adenopathy may be placed *simple adenopathy*. I must confess that, for my own part, I am inclined to hold many of these so-called simple adenopathies as akin to the tuberculous. Yet it may be granted that in some cases, and particularly in youth, inflammatory diseases of the respiratory organs are apt to induce glandular hypertrophy. The glandular enlargement of leucocythæmia need only be mentioned here, as its consideration belongs to another article in this work.

Etiology.

Little or nothing can be said of the etiology of mediastinal tumors. Traumatisms have now and then been mentioned, and it has also been said that repeated slight shocks are capable of inducing some degree of irritation of the region, and so determining the localization of cancer or tuberculosis. But all that is exceedingly vague, and leads to no positive conclusion.

Prognosis.

This is decidedly gloomy when the tumors, whatever their nature, are bulky and tend to invade neighboring organs.

Treatment.

The treatment should be symptomatic, and, when possible, conducted so as to meet the indication furnished by the patient's diathesis.

Any attempt at surgical interference is, of course, inadmissible in these cases.

For the cough, antispasmodics and narcotics may be administered: aconite (the tincture of the root), belladonna, hyoscyamus, and the preparations of opium. If the pain is sharp, recourse may be had to hypodermic injections of morphine, a remedy which can rarely be dispensed with in the advanced stages of these affections.

In cases of tuberculosis or of simple adenopathy, iodine and arsenic may be tried successively. The tincture of iodine should be taken, at bed-time, in milk in order to spare the stomach. The arsenic may best be given in the form of Fowler's solution. Tonics must not be omitted, such as cod-liver oil, phosphate or rather glycerophosphate of lime, cinchona, etc.

Some patients are improved by the mineral-water treatment with the sodic chloride waters of Salies de Bearn, or of Salins; and I should here mention the sea-weed baths at Lut-sur-Mer, on the coast of Normandy. Marked benefit has, to my own knowledge, been derived from a combination of these remedies, and the progress of the disease has thereby been delayed. It is needless to remark that I make no reference to cancer, against which no treatment at present known to us can avail.

Abscess.

Properly speaking, these abscesses belong to the domain of surgery, and consequently do not come within the sphere of this article. We may, nevertheless, devote a few lines to them, in order to complete the review of the diseases of the mediastinum.

Authors have divided these abscesses into idiopathic and symptomatic, the latter being by far the more common. Notwithstanding a few cases, somewhat obscurely described, I am not quite sure whether it is possible to find any such as an absolutely idiopathic abscess of the mediastinum. Symptomatic abscesses are due to osteitis —caries of the sternum, for instance—or to propagation from another purulent focus, a phlegmon of the neck, empyema, etc.

The *diagnosis* of these abscesses is always doubtful at first, even in case of propagation from another focus. But sooner or later special signs appear, retrosternal pains, oppression, difficulty or em-

barrassment of respiration and circulation, with possibly œdema and cyanosis, and fever, with chills and sweats. Finally, the collected pus makes its way to the surface in not a few cases.

The only *treatment* available for a mediastinal abscess, whatever its cause, is to puncture the abscess as promptly as possible, after the diagnosis has been fixed. Large incisions, drainage, even trepanning of the sternum, accompanied by rigorous antisepsis and careful dressing, are the only means to be employed. The patient's constitution should in the mean time be sustained by use of the different tonic agents.

The subject of *foreign bodies* in the mediastium is one that belongs wholly to the domain of surgery, and its discussion need not be entered upon here.

DISEASES OF THE DIAPHRAGM.

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DISEASES OF THE DIAPHRAGM.

Few of our classical treatises on internal pathology contain any chapter devoted to the consideration of diseases of the diaphragm. Here and there in the articles relating to the thoracic or abdominal organs we may find reference to some symptoms of diaphragmatic affections, but they are generally mentioned as secondary symptoms of the disease under consideration. It is only in encyclopedic works or in special monographs that we find particular mention of the diseases involving the diaphragm. The reason of this semi-obscurity is easy to understand. In order to study apart the diseases of the diaphragm we are obliged to make an entirely artificial classification subservient to the needs of this description. Indeed, the affections of the diaphragm which we may call essential or absolutely primary are very few in number, if they exist at all, and the lesions of this part are most frequently, if not always, secondary to some other general or local disease. Nevertheless it is useful to direct special attention to the diaphragm and to study somewhat in detail its diseases in order to gain a more clear notion of the pathology of this muscle. Our work will be chiefly that of an analyst, dwelling upon a train of symptoms forming part of a descriptive whole and noting those which belong to one or another disease.

The diaphragm is a muscular organ which forms a vaulted partition between the abdominal and thoracic cavities, and is one of the most powerful of the physiological agents in the mechanism of respiration. By reason of its position it is exposed to invasion by the diseases affecting primarily one or other of the neighboring organs; it is liable to suffer from certain other affections in its quality of a muscle; it suffers from affections of motility from the fact that it is an important organ of respiration, powerfully innervated, these disorders proceeding most frequently from diseases of the central nervous system or from neuroses; finally, it may suffer directly from traumatism.

This enumeration serves as the basis of the classification, altogether artificial, which we shall here adopt in order to pass in review the various affections of which the diaphragmatic muscle may be the seat.

Traumatic Affections.

Wounds.

Wounds of the diaphragm may be produced by various agents, either a cutting instrument or a firearm; but in whatever way produced, the diaphragmatic wound is usually of quite secondary importance, for this organ is seldom or never, if we except a few reported cases, the one primarily or mainly affected. There is always at the same time a wound or a contusion of one or more of the neighboring organs, such as the lungs or one of the abdominal viscera, and the diagnosis, as well as the prognosis, rests much more upon the signs of injury to these organs than it does upon any symptoms pointing specially to involvement of the diaphragm.

The patient, if seen soon after the receipt of the injury, is in a state of shock, more or less intense, such as is characteristic of all severe traumatisms involving important organs. The face is contracted, the nose pinched; the respiration is perhaps more or less embarrassed; the pulse is small and thready.

We need hardly say that the prognosis is, in most cases of injury of this sort, very grave.

The treatment offers no points upon which it will be profitable to dwell, for it presents nothing in particular, being simply and solely that indicated by the injury of the neighboring organs, and that furthermore of the shock which has received sufficient consideration in another volume of this work.

Rupture.

Lacerations and ruptures of the diaphragm might well have been described with penetrating wounds, for although it is customary to devote separate sections to these two classes of injury there is no clinical reason for so doing, the symptoms of the two conditions being practically identical. Lacerations of the diaphragm may be determined by various causes, by a violent blow directly against the lower portion of the chest, by a fall, or other injury, but the most frequent cause is fracture of a rib with displacement of a sharp fragment and consequent penetration of the diaphragm.

The symptomatology of laceration of the diaphragm is somewhat complex. When the rupture is considerable and is the result of a very severe injury, we find the symptoms of shock and collapse, with small pulse and the risus sardonicus which was long ago regarded as a characteristic symptom of affections involving the diaphragm.

If the tear or rupture is less extensive the symptoms may be correspondingly milder, and the prognosis consequently less grave. There may be then simply a pain at the level of insertion of the diaphragm and sometimes the signs which we shall come to recognize later as pointing to neuralgia of this muscle. We need not dwell longer upon the injuries of the diaphragm and may proceed at once to study the diseases to which it is subject by transmission from neighboring organs.

Affections Transmitted from Neighboring Organs.

Adhesions.

It is not unusual at autopsies to find adhesions of the diaphragm to neighboring parts, either of the thorax or of the abdomen. In most cases they consist of more or less elastic bands which yield somewhat to traction so that the attached organ is not held in close apposition to the diaphragm. Occasionally, however, the adhesions, long or short as the case may be, become encrusted or infiltrated with calcareous salts, and are then hard and unyielding.

The adhesions (to the pleura, pericardium, or peritoneal investment of the stomach, intestine, liver, or spleen) are usually consecutive to a previous inflammation of the affected serous membrane. The pleural adhesions may cause impeded respiratory movements, but the most pronounced symptoms are those occasioned by adhesions between the diaphragm and the pericardium occurring in pericarditis. Inspection then shows undulatory movements in the epigastrium which are isochronous with the cardiac pulsations.

Perforation.

Ulceration and perforation of the diaphragm are most frequently the result of burrowing of pus either from above downwards or from below upwards. The pus may come from a pleuritic or a pericarditic abscess which discharges into the abdominal cavity, after perforating the division wall, and gives rise to a usually fatal peritonitis; or it may be from a purulent collection in the liver which takes an upward course and empties into the pleural cavity or even pierces the lung and is then coughed up. These are all, however, merely pathological curiosities.

Displacements.

More or less extensive displacements of the diaphragm are, as opposed to the condition just mentioned, not very uncommon. It

can be readily understood how this muscle may be displaced, how the diaphragmatic vault would be increased or lessened according to the varying or abnormal development of the viscera on one or the other side of it. If the heart become largely hypertrophied or the pericardium become distended with fluid, the muscle which is called upon to support this increased weight is depressed. Alterations in size of the liver also necessarily change the position of the diaphragm, but the effect varies according to the degree of enlargement which the liver has undergone. When there is moderate hypertrophy the convex surface of the organ rises and pushes up the diaphragm before it, but when the weight of the liver is greatly increased by a cancerous growth or in hypertrophic cirrhosis, it falls lower in the abdomen and, pulling strongly upon the diaphragm through the suspensory ligaments, causes this muscle to be depressed to sometimes a very considerable extent, and with it often is dragged down the heart as well. On the other hand the stomach, becoming distended with gas, may push the diaphragm upwards.

Another variety of diaphragmatic displacements is that due to diseases of the spinal column, accompanied by kyphotic deformities of this part. Under the influence of deviations or caries of the bodies of the vertebræ the diaphragm loses more or less of its symmetry and its vault tends to become more shallow. The displacements thus imposed upon it may react upon the heart, so that this organ may be changed in its position, becoming almost horizontal. In these patients also the circulation is impeded at the same time in consequence of the altered relations of the great vessels in the first part of their course.

Tumors.

The recorded cases of tumors of the diaphragm are few in number, and our knowledge of such is very imperfect. Those that have been reported belong to the class of post-mortem findings, for the diagnosis was not made during the life of the individual. Grancher has reported a case, quoted in all the French works on this subject, of a tumor of the diaphragm which was entirely independent of all other structures, a true primary diaphragmatic tumor.

The extension of tumors to the diaphragm from neighboring organs is of much less infrequent occurrence. A cancer of one of the adjacent abdominal or thoracic viscera not uncommonly extends by continuity to the diaphragm. Hydatid cysts in like manner often involve the diaphragm secondarily.

Finally certain forms of *degeneration* have been observed in the diaphragm, and especially ossification of the muscle, the latter being

of uncertain cause but in some cases seeming to be excited by the irritation of a pleurisy.

Affections of the Muscular Structure.

We have now to consider the diseases which may attack the diaphragm primarily in its character as a muscular organ. The affections which we shall consider will be rheumatism, inflammation, and atrophy.

Rheumatism.

Like all other muscles, the diaphragm may be the seat of a rheumatic process. Three forms of diaphragmatic rheumatism have been described: (1) Acute primary, (2) acute secondary, and (3) chronic. We need not here dwell upon the etiological factors which may determine an attack of diaphragmatic rheumatism; given the individual predisposition, cold and damp appear to be the chief exciting causes of the affection.

Symptoms.—In the acute primary form the patient is attacked suddenly, usually after a chilling of the surface. He has violent pain in the lower part of the chest at the level of the insertion of the diaphragmatic muscle. On palpation carefully made, firm pressure being applied by the examining finger, it will be found that the pain exists all around the thorax in its lower part; this pain is generally symmetrical, although not invariably, for we sometimes encounter a diaphragmatic rheumatism which is more or less unilateral in its location. This latter is, however, exceptional, and the presence of bilateral and symmetrical pains in the lower portion of the chest speaks quite strongly in favor of a diaphragmatic rheumatism. Auscultation furnishes negative evidence only; there are no râles to be heard (in the absence of a complicating pulmonary trouble) nor any other adventitious sound, but at the base of the lungs the respiratory murmur, as might be expected, is usually feeble. The movements of the diaphragm being productive of pain, the patients seek to restrict them as far as possible, and thus the respiratory movements are confined almost entirely to the upper portion of the thorax, and are in consequence much less extensive than in the normal condition.

Movements of deglutition are also painful, and in addition to a more or less persistent hiccough there may be œsophageal or even laryngeal spasms, which are probably of reflex origin. The pain is not always of the same intensity, but appears to occur in the form of crises of longer or shorter duration.

There are no general symptoms, neither elevation of temperature nor acceleration of pulse.

In the secondary form of acute rheumatism of the diaphragm, the affection appears in the course of an acute articular or muscular rheumatism. The symptoms are the same as those of the primary form, except that we see here an elevation of temperature due to the general condition.

In chronic diaphragmatic rheumatism the pain does not occur in paroxysms, as in the acute forms, but is obstinate and persistent, being always complained of; it interferes with the respiratory movements, and in certain very severe cases it has been followed by grave complications due to paralysis of the diaphragm.

Prognosis.—It is only in these grave forms that the prognosis is at all serious, for in the immense majority of cases diaphragmatic rheumatism is a benign affection, from which recovery takes place without any serious complications or sequelæ.

Diagnosis.—The affection must be differentiated from all forms of pleural and pulmonary inflammations and from neuralgia. Careful auscultation will enable us to exclude disease of the lungs or pleura. Intercostal neuralgia is that which is most liable to be confused with rheumatism of the diaphragm, but a differentiation may usually be made by the fact that the former is as a rule unilateral, and also that the pain is commonly most intense at the three points of emergence of the superficial branches. A mistake in diagnosis might be possible in the case of angina pectoris or of asthma, but a careful study of the symptomatology ought to prevent an error of this nature.

Treatment.—The local treatment of diaphragmatic rheumatism is to be conducted on the same plan as that of muscular rheumatism elsewhere. The pain may be relieved by local revulsives, such as tincture of iodine, or in very severe cases and when we wish to obtain a rapid effect we may resort to wet cupping. Antipyrin or morphine by hypodermic injection may be required; the latter, when made in the vicinity of the painful parts, may afford speedy relief.

The general treatment consists in the administration of the approved antirheumatic remedies, such as sodium salicylate, salophen, salicin, and the like.

Diaphragmatitis.

There is little to be said concerning the affection to which this name has been given, namely, primary inflammation of the muscular tissue of the diaphragm. The most recent works bring no new light to illuminate the subject, and it is difficult to decide whether we ought to reject absolutely as non-existent such a pathological entity, or to admit that such an affection may, though rarely, be observed. It is certain that muscular tissue in general is subject to

inflammatory processes, and reasoning from the general to the particular we ought to admit the possibility of inflammation of the diaphragmatic muscle. But the fact that such an affection has never been recognized clinically throws doubt upon the possibility of its occurrence and involves the entire subject in an obscurity from which it possibly may never emerge.

It is true that pathological anatomy has shown us the presence of lesions attributable to an inflammatory process, but there has always been at the same time an inflammation of one of the adjacent serous membranes, either the peritoneum or the pleura, and the diaphragmatic inflammation may well have been simply secondary to this pleurisy or peritonitis. My belief is, however, that we are not justified in excluding from medical pathology primary diaphragmatitis, for inflammation of this muscle may undoubtedly exist, and it has repeatedly been seen as a secondary process after traumatisms and as a result of neighboring inflammations; but it possesses no individual symptomatology, for the signs of its existence cannot be distinguished from those of pleurisy, peritonitis, or inflammation of one of the organs lying immediately above or below the diaphragm. And for the same reason there is nothing to be said concerning the diagnosis and treatment.

Atrophy.

Atrophy of the diaphragm has been observed in the course of various diseases affecting the muscular system in general. Whether the affection be of spinal or of purely myopathic origin, the diaphragm may be affected as well as any other of the muscles; but by reason of the important function of this particular muscle, its implication is of greater moment and productive of more serious consequences, for atrophy may so gravely interfere with the respiratory movements that the most distressing asphyxia and even death may ensue. This is what happens when the atrophy reveals itself clinically, but it may also be a purely post-mortem discovery, having existed during life without giving rise to the slightest symptom; and this is what most frequently occurs, the diagnosis being made only at the autopsy, and sometimes only with the aid of the microscope. Pathologists have thus distinguished various forms, such as simple atrophy, atrophy with granular degeneration, with waxy or hyaline degeneration, but such refinements are of absolutely no clinical value, and may well be left to works dealing purely with pathological anatomy or rather morbid histology.

The diseases in the course of which atrophy of the diaphragm may occur are quite numerous. We need not refer again to the essential

or other forms of myopathy, of which we have just spoken, but would mention the diseases of the respiratory or circulatory apparatus which may be accompanied by the condition now under discussion. Atrophy of the diaphragm may thus be met with in autopsies on persons dead of chronic bronchitis, of emphysema, of interstitial pneumonia, of degenerations of the myocardium, or of pericarditis. It is usually after certain of these chronic affections have existed for quite a length of time and have induced a marked degree of weakness or even a cachectic condition, that we first observe signs of atrophy of the diaphragm. We can readily understand how this atrophy must hasten the fatal termination by diminishing the respiratory powers and thus leading to a more speedy occurrence of asphyxia.

Nervous Affections.

We have now to consider those affections of the diaphragm which are due to disturbances of innervation of this muscle, under which group come paralysis, spasm, and neuralgia.

Paralysis.

Paralysis of the diaphragm is observed in the course of a great number of affections of various nature. It has been seen as a result of direct injury to the spinal cord or phrenic nerve, in diphtheria, lead poisoning, inflammatory affections of the pleura or lungs, and in hysteria. The gravity of the condition may vary according to the circumstances, but whatever may be the form, paralysis of the diaphragm is always a serious affection because of its interference with the respiratory functions and of the very grave consequences which may ensue.

Symptoms.—In different cases of paralysis of the diaphragm the symptoms may vary greatly, in one case the diagnosis being only too evident, in another the condition escaping the attention of the physician unless he think of the possibility of its occurrence and direct his examination in consequence particularly to this muscle. The paralysis may be unilateral or bilateral, and the resulting disability may be complete or partial. As a type for our study, we shall consider a patient attacked with complete bilateral paralysis. At the first glance it will be seen that the patient is suffering from difficulty in breathing, from dyspnœa. If he change his position or make any effort whatever the dyspnœa will be at once greatly increased. If any question be addressed to him his reply will be in a feeble voice, interrupted at every word with the necessity for taking a breath. On uncovering the chest and abdomen of the patient one

will at once be struck with the changes in the visible respiratory movements; the respiration is reversed, and the abdomen, instead of rising during inspiration, sinks in; but in expiration the opposite occurs. This reversed movement is easily explained by the loss of the active participation of the diaphragm in the act of respiration; instead of assisting in the respiratory movements, it is, during inspiration, sucked up, as it were, drawn up into the thorax, and from this follows the sinking in of the epigastrium instead of its bulging out during inspiration; in expiration, on the other hand, the compression of the lungs by the thoracic muscles pushes down the diaphragm and there is a bulging of the epigastrium. This reversal of the ordinary respiratory movements of the abdomen is the essential symptom of diaphragmatic paralysis, and the one upon which we have to rely in our diagnosis of this condition. But although it is very evident in certain cases and impossible of being overlooked upon inspection of the abdomen, yet in others it may escape detection unless special attention be directed to the search for it. This occurs particularly in cases of unilateral paralysis, when the loss of power on one side is, under ordinary circumstances, compensated for by the action of the unaffected side. We must then cause the patient to make deep and forced inspiratory movements, when the changes above noted will become very apparent on the affected side, while the normal respiratory movements of the epigastrium will be seen on the sound side. In order to render the diagnosis more easy we ought always to examine the patient after exercise, for during sleep or complete repose, when the respiratory movements are normally but slightly apparent, we may fail to detect any difference in this respect between the two sides.

Prognosis.—It is hardly necessary to insist upon the gravity of this condition, even when it is apparently of slight degree; in cases of complete bilateral paralysis asphyxia may ensue upon the slightest extra call on the respiratory organs, even that arising during a mild cold in the head. Although always of possible gravity, the prognosis will necessarily vary greatly according to the degree of paralysis and the extent of the diaphragmatic muscle involved.

Treatment.—This should be addressed as far as possible to the cause of the paralysis; in the case of plumbism, for example, our efforts should be directed towards securing an elimination of the poison as soon as possible from the system. But in many cases, especially when the affection is of spinal origin, the general treatment will be productive of little or no benefit.

The local treatment will consist simply in the employment of electricity. Duchenne, of Boulogne, who has especially studied

these paralyses, advised local faradization, and it is this mode of employment of electricity to which we ought always to have recourse in a case of paralysis of the diaphragm.

Spasm.

Spasm of the diaphragm as a morbid entity is rarely observed, and more often it is secondary to some general disease, especially of one of the neuroses. We distinguish tonic and clonic spasms of the diaphragm, the former being of a much more serious nature than the latter.

Tonic Spasm.

Tonic convulsions of the diaphragm may be either idiopathic or symptomatic. An instance of the former has been related by Duchenne. A player on the bassoon was suddenly, without any apparent cause, seized with a spasmodic contraction of the diaphragm, which prevented him from following his occupation, for sometimes there was an inspiratory spasm which forced him to aspirate the air from his instrument, thus producing no sound, and at other times an expiratory convulsion of the diaphragm forced an explosion of loud sound from the bassoon.

The symptomatic tonic spasms are encountered chiefly in epilepsy, tetanus, eclampsia, asthma, rabies, and in strychnine poisoning. The sign by which we are enabled always to recognize the tonic convulsion of the diaphragm is the altered respiration. The thoracic cage is enlarged at its base, and the respiratory movements take place only in the upper portion of the chest. Dyspnœa and suffocative attacks are of course present. The patient complains of a girdle pain, has a sensation of constriction, and, if the spasm continues, begins to suffer the agonies of asphyxia. At this time auscultation reveals a diminished vesicular murmur.

When the convulsion is of short duration the patient speedily returns to his normal state after a few deep inspirations and expirations, but if the spasm continue, as in infantile eclampsia for example, the patient dies asphyxiated.

The *treatment* consists in energetic counter-irritation over the epigastrium, on the sides of the thorax, and in the dorsolumbar region. For this purpose there have been used compresses wet in boiling water, punctate cauterizations, and wet cups. It is necessary to administer at the same time antispasmodics, such as ether, valerian, the bromides, etc.

Clonic Spasm.

The existence of idiopathic clonic convulsions of the diaphragm has not been positively established, and we need occupy ourselves here only with the symptomatic forms. It is with the clonic as with the tonic spasms of the diaphragm, the accompanying affection is most often a neurosis, such as hysteria, epilepsy, or eclampsia, but the spasms have been noted also in several febrile affections and in certain diseases of the spinal cord.

Clonic spasms of the diaphragm are revealed by movements of rising and falling in the epigastric and hypochondriac regions, which vary in extent and frequency. In some cases they occur with such frequency that there seems to be a tremor of the epigastric region. When their extent is considerable the diaphragm strikes convulsively the adjacent viscera, in the course of its exaggerated inspiratory excursion; the stomach and intestines are pushed suddenly downwards, and sometimes there is a sort of succussion sound produced with each inspiration, while at the same time the eye may perceive a rapid and sudden elevation of the entire abdominal region. The phenomenon known as hiccough accompanies clonic spasms of the diaphragm. Speech is interrupted and the peculiar inarticulate sound is heard with each successive convulsive movement. There may even be sobbing, and sometimes the strong pressure on the stomach causes vomiting.

When these clonic convulsions are of short duration the patient is not particularly disturbed by them, and returns at once to his normal condition upon their cessation; but when they persist for a long period, there is often pain, the patient complains of great fatigue, and he is frequently deprived of sleep.

The *prognosis* depends upon the duration of the attack, but the affection does not threaten the patient's life directly as may tonic spasm of the diaphragm. When of very long continuance, clonic spasms may affect the patient injuriously in an indirect way by interfering with digestion and with the assimilation of food, if they are of such severity as to cause vomiting or the regurgitation of food. That is recognized as one of the chief dangers to the little patient from whooping-cough, for the vomiting resulting from the cough and the diaphragmatic spasm sometimes renders alimentation impossible, and the child emaciates and dies of slow starvation.

The *treatment* is to be directed to the general condition as well as against the spasmodic state itself. I need not dwell here upon the general treatment, as that will receive full consideration in the articles in this work which treat of the causal maladies, those on hysteria,

epilepsy, etc. Among the measures directed against the spasmodic contractions of the diaphragm, pressure at the pit of the stomach, either manual or instrumental, appears to have given good results in certain cases. Refrigeration of the same region by means of ether sprays, the application of a small blister, and faradic electrization are other remedies which have been employed. The latter, which is perhaps the most effective of those mentioned, may be practised over the two phrenic nerves by placing one electrode over one nerve and the other over that of the opposite side, or one nerve only may be faradized, one electrode being placed over it and the other at the insertion of the diaphragm.

Neuralgia.

In treating of neuralgia of the diaphragm we pass from the study of a disease of muscular tissue and enter upon that of an affection of the nerves, yet the malady concerns so closely the structure which we have been considering that it calls for brief mention among the diseases of the diaphragm.

The *causes* are those common to all forms of neuralgia, to wit, a chilling of the body, the rheumatic diathesis, and diseases of neighboring organs; of the latter diaphragmatic pleurisy and pericarditis are among the most frequent.

The main *symptom* is pain in the neck along the course of the phrenic nerve and at the base of the thorax at the points of insertion of the diaphragm; sometimes we find pain radiating to the shoulder, which is one of the most common accompaniments of diaphragmatic pleurisy. The functional signs are simply those resulting from the interference with respiration caused by the neuralgic pain, which is aggravated by any increased respiratory movements.

The *treatment* must be directed first against the general disease. Locally, we may make use of revulsives or hypodermic injections of antipyrin or morphine, though we must be cautious in the use of the latter drug in an affection which is apt to be so obstinate as this.

DISEASES OF THE BLOOD.

BY

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DISEASES OF THE BLOOD.

THE BLOOD.

In an anatomical sense the blood may be looked upon as a tissue composed of cells and a fluid intercellular substance. In a physiological and biological sense, however, there is a most important difference between this and other tissues. All of the tissues enjoy a more or less pronounced independence, growing by cell multiplication and exercising specific functions locally or upon the economy through the blood or in other ways. Such independence is wanting to the blood. The reproduction of its cellular elements occurs in specific organs, and the integrity of its intercellular or fluid part is dependent upon the general systemic metabolism, upon the state of the fixed tissues, the proper maintenance of the circulation, etc. The blood is therefore in every respect a subservient tissue, if we may call it a tissue at all. Its diseases are rather results of underlying derangements of other structures than primary disorders, though we are often entirely in the dark regarding the primitive disturbances, and rarely understand the exact manner in which alterations or disorders of the blood itself are produced.

The blood is a liquid of red color, rather viscid, and of alkaline reaction. It consists of a watery or fluid part, the *liquor sanguinis*, or *plasma*, an albuminous and saline liquid; and cellular elements or *corpuscles*. The latter are of three kinds: red corpuscles or *erythrocytes;* white corpuscles, colorless corpuscles, or *leucocytes;* and *blood plaques*. The red color of the blood is due to an albuminous and iron-containing pigment called *hæmoglobin* which is found in the red corpuscles and makes up the greatest part of their bulk. In the arterial blood this is combined with oxygen forming oxyhæmoglobin, to which the bright-red color of this blood is due; in the venous blood much of the oxygen has been abstracted and the *reduced hæmoglobin* gives a darker color to the blood. Other changes occur in the saline constitution and the amount of water, but the changes in the hæmoglobin are most important. When blood escapes from the body, clotting or coagulation usually occurs in a few minutes and a solid clot is formed. This consists of a meshwork of fibrin, entan-

gling red corpuscles more or less abundantly according to the way in which the clotting has occurred. After a time the clot contracts and a clear liquid of red color is expressed and lies above the clot in the vessel in which coagulation has occurred. This liquid is the *serum* of the blood.

The *total quantity* of the blood is not easily determined, and probably differs in different persons of the same weight, as it differs in various animals. The normal quantity is ordinarily considered to be about one-thirteenth of the body weight.

Blood Formation.

The process of blood formation, though it has been studied with the greatest zeal by nearly all of the distinguished histologists, remains exceedingly obscure in a number of particulars. Certain facts, however, have been discovered and are accepted by nearly all authorities. It is admitted that during early embryonic life the red corpuscles first make their appearance in the mesoblastic columns which go to the formation of the vascular channels. These columns are solid masses of cells in the midst of which certain nucleated forms are observed. These in the earlier stages contain no coloring matter but later become pigmented with hæmoglobin. In this manner a nucleated hæmoglobin-containing corpuscle is formed, while the surrounding cells become differentiated to form the walls of the vascular channel. Subsequently for a certain period all of the blood corpuscles have the same appearance and are formed in a similar manner within the primitive blood-vessels, the reproduction of the cells taking place by karyokinesis. These facts were first developed by Kölliker. At a subsequent period, according to Neumann, the liver becomes an important seat of hæmogenesis, red blood corpuscles having appearances like those of the forms previously described originating within the venous capillaries of this organ. At this stage it is maintained that the liver is the important seat of hæmogenesis. About the same time or later the white corpuscles first make their appearance in the blood. The spleen comes into activity at about the fifth month and takes the place of the liver, which grows gradually less active. Finally, the bone marrow is concerned with the formation of the red corpuscles during fœtal life and for some time before birth; and after birth it becomes the most important seat of hæmogenesis. During the period in which the spleen and bone marrow have become active the nucleated red corpuscles grow less abundant and finally disappear entirely from the blood so that at birth they are rarely found. The important part played by the bone-marrow in the

formation of the red corpuscles was independently observed and described by Neumann and Bizzozero in 1868, though the latter has more frequently received the credit for it. These observers noted the abundance in the marrow of nucleated red corpuscles and looked upon these as the progenitors of the fully developed erythrocytes.

The views thus far detailed have been accepted by the majority of hæmologists; but regarding certain details and regarding the seat and manner of development of certain of the cells alluded to, difference of opinion still exists. For example, the manner in which the nucleated corpuscles become converted into non-nucleated red cells has given rise to much discussion.

According to Bizzozero and Neumann the nuclei of the erythroblasts gradually undergo disintegration and thus disappear. This view has recently been defended by Freiberg in his inaugural dissertation. On the other hand, Rindfleisch and Howell insist that the nuclei are extruded from the cell and for a time circulate as free nuclei, and the former observer with Fellner claims to have observed this process actually taking place, while Howell explains the concavity of the red cells by the assumption that the escape of the nucleus leads to a sinking in of the centre of the disc. Ehrlich has united both views and holds that the small nucleated erythrocytes (normoblasts) extrude their nuclei, while the nucleus of the megaloblast disappears by disintegration. Notwithstanding the fact, to which Neumann and others have directed attention, that the extrusion of the nucleus noted by certain investigators has been due to the mechanical or chemical influences under which the investigations were conducted, it seems certain that the nuclei frequently do escape in this manner, as I have observed in fresh blood beneath the cover-glass. It is quite likely, however, that such extrusion is exceptional and unessential.

Regarding the place of origin of the nucleated corpuscles, Bizzozero found that they are produced in the venules of the bone marrow, which may frequently be found to contain abundant erythroblasts, presenting mitotic figures. This view has been confirmed by Mackenzie and Galloway, by Freiberg and others. Difference of opinion, however, exists as to the origin of these cells in the marrow, Bizzozero holding that the nucleated corpuscles invariably arise by nuclear division from pre-existing cells of the same kind, while a number of other observers believe that the hæmatoblasts or primitive nucleated red cells are formed from non-pigmented marrow cells by the gradual assumption of hæmoglobin.

While, however, this pre-eminence of the bone marrow is generally admitted, the fact must not be lost sight of that the spleen, the

lymphatic glands, and the other lymphadenoid structures do take a part in blood formation in post-embryonal life. This was asserted for the spleen by Bizzozero, Salvioli, and Eliasberg, the latter calling attention to the abundance of nucleated red cells in the spleen after hemorrhage; and by Löwit, Müller, and Wertheim for the lymphatic glands.

It may be well at this time to notice briefly some of the more important theories regarding the primitive origin of the red corpuscles.

The theory of Löwit has received a great deal of attention, though it has not been generally accepted. This observer maintained that the red and white corpuscles are formed in two separate series, the one having no connection whatever with the other; and he holds that the spleen, the marrow, and the lymphatic glands are concerned almost in equal degree in the formation of the blood corpuscles. The red corpuscles originate from certain cells, designated *erythroblasts*, which divide by karyokinesis and present no amœboid movements of their protoplasm; while the leucocytes originate from *leucoblasts* which invariably divide by direct division (*divisio indirecta per granula*) and present evidences of amœboid movement of the protoplasm.

H. F. Müller and Wertheim hold that the white and red corpuscles have a common origin in the blood, spleen, lymphatic glands, and bone marrow, the common mother cells dividing by mitosis and giving rise to red corpuscles or to polymorphous leucocytes. In the formation of the latter, the cells formed by the division of the primitive mother cell are mononuclear *leucoblasts*, resembling the original mother cell but becoming subsequently converted into polymorphous white corpuscles. The red corpuscles may be formed directly from the primitive mother cell by the appropriation of hæmoglobin, or indirectly from secondary or daughter cells of the same generation as the leucoblasts.

Hayem has maintained the theory, which has been largely accepted by the French hæmatologists, that the red corpuscles in large part originate from the blood plaques or, as Hayem terms them, the *hæmatoblasts*. This view was suggested by the fact that the latter formations are particularly abundant in the blood during processes of regeneration, and Hayem describes corpuscles which seem to illustrate a gradual transition of the plaques into red corpuscles. The origin of the hæmatoblasts themselves is supposed to be from the white corpuscles within the lymphatic channels. This theory, however, has received little confirmation and has been practically disproved by Bizzozero, Neumann, and others.

The origin of the white corpuscles is quite differently interpreted by different investigators. The views of Löwit and Müller are suffi-

ciently detailed in the foregoing. Other observers, however, deny that there is any connection between these and the red corpuscles. At the present time this is the prevailing view. The origin of the leucocytes, however, is sufficiently obscure without considering their relations with the erythrocytes. Virchow first called attention to the small mononuclear forms and the larger elements, and held that the former originate in the lymphatic glands, while the latter spring from the spleen. He distinguished the conditions *lymphæmia* and *splenæmia*, according as one or the other leucocytic form is abundant. Such a distinction has been maintained even in recent years, though the investigations of Löwit, Arnold, and others have established the fact, now quite generally recognized, that the small mononuclear forms or lymphocytes are the youngest white corpuscles and may originate in the lymphatic glands, the spleen, or the marrow, while the larger forms and the polymorphous elements are direct or indirect derivatives. In the spleen and in the lymphatic glands the formation of the leucocytes takes place by karyokinesis, the Malpighian bodies and the lymphatic follicles being the centres of development—*germ centres* (Flemming). The lymph contains abundant small mononuclear forms which have thus originated. These subsequently enlarge and probably pass through a more or less regular cycle of life. In this transformation the blood-making organs doubtless exercise a second function. Ehrlich and his followers have sought to determine the process of leucocytic development by the methods of color analysis, but thus far these studies have failed to show in what situations and in what manner the transformations occur. It is quite certain that the changes do not take place in the blood itself; and it is probable that the bone marrow plays an important rôle. The eosinophile leucocytes, at one time regarded by Ehrlich as myelogenic in origin, are certainly not the exclusive product of the marrow. The large colorless cells occasionally met with in disease and known as myelocytes do seem undoubtedly to be marrow cells in the strictest sense of the word.

The maintenance of the plasma is dependent upon the integrity of the various organic functions, and its condition is undoubtedly influenced, though often but little, by every disturbance of the physiological processes.

Composition of the Blood as a Whole.

The specific gravity of the blood has been determined by a large number of observers. The degree of density depends upon the quantity of water and also upon the amount of solid residue. The addition or abstraction of water from the circulating blood may occur

under diverse conditions, affecting the circulation, the metabolic activities of the tissues, and other functions, and the change in specific gravity may be very considerable. Normally this varies at different ages and in different individuals, between the limits 1.040 and 1.065. The average, however, may be taken to be somewhere about 1.055. At birth Jones found it 1.066, but the density sinks rapidly and by about the second year it falls to the minimum, from which there is a gradual and progressive ascent throughout life. The amount of water in the total blood varies from 76 to 80 per cent., the solid residue being from 20 to 24 per cent.

Among the important constituents are the albumins and other nitrogenous substances. Of the albumins the hæmoglobin of the red corpuscles, the serum-albumin and serum-globulin of the serum, and the remaining albuminous substances of the corpuscles are important. The relations of these are considered in the discussion of the corpuscles and the serum. Under abnormal conditions it has been held by a number of observers that peptone may occur in the blood, and in particular this has been claimed for leukæmia. Recent investigations, however, would seem to indicate that the peptones described have been either albumoses mistaken for peptones or post-mortem developments. True peptone in the sense of Kühne has never been satisfactorily demonstrated (see Leukæmia).

Among the nitrogenous substances uric acid occurs in traces in the normal blood, but may be found in considerable proportion in certain diseases, notably in gout, leukæmia, and other anæmias. This has been ascribed to decreased oxidation, but the explanation does not suffice in many instances. The close relation of uric acid to leucocytic destruction, particularly to disintegration of the nuclei of the white corpuscles, has recently occupied much attention; and in leukæmia and in leucocytosis the proportions of uric acid in the blood undoubtedly bear a direct relation to the destruction of leucocytes. Such a destruction may occur in the blood itself, and Neusser has recently pointed to certain demonstrable changes in the leucocytes suggestive of such destruction in the blood or within the tissues of the body.

Urea may appear in the blood in large quantities in cases of nephritis and particularly during uræmia as well as in fevers. Ammonium occasionally occurs in small amounts. The so-called xanthin bases, hypoxanthin and xanthin, have been found particularly abundant in leukæmia. The presence of increased quantities of these bodies has the same significance as excess of uric acid, the production of all of these substances occurring when cellular disintegration takes place.

Among the inorganic constituents of the solid residue of the blood, chlorine, potassium, sodium, and iron are of the greatest importance.

The total quantity of inorganic substances according to Schmidt's analyses constitutes 5 per cent. of the entire bulk of the blood, while the total residue is 17.5 per cent. The percentage of chlorine varies from 27 to 31 or more per cent. of the total ash, the potassium from 17 to 21, the sodium from 22 to 28, and the iron from 5 to 6 per cent. These proportions vary considerably in different diseases (see Anæmia).

Carbohydrate substances, notably grape sugar and glycogen, are found in small proportions. The former of these is met with in large quantities in diabetes and according to Freund and Trinkler in carcinoma. Glycogen appears to occur in the leucocytes of the blood as in pus and also to a certain extent in the plasma of the blood. The nature of the substances looked upon as glycogen within the leucocytes has, however, been questioned.

A glycolytic ferment and a diastatic ferment are met with in the blood in various conditions. The former is regarded as of particular significance in the pathology of diabetes by Lépine.

Fatty acids are occasionally present in small traces (*lipacidæmia*). Von Jaksch has frequently met with them, particularly in cases of fever, leukæmia, diabetes, and acute yellow atrophy of the liver.

Fat (see Lipæmia), cholesterin, lecithin, and soaps are normal constituents.

The gases of the blood include oxygen, carbonic oxide, and nitrogen. The amount of oxygen decreases and the CO_2 increases in venous blood. The latter forms combinations with the saline constituents, especially with the sodium; the former is mainly in association with hæmoglobin.

The alkalinity of the blood varies somewhat in different conditions, though the unsatisfactory character of the methods thus far devised prevent positive deductions from the experiments recorded. It is dependent in the largest measure upon the presence of sodium in the form of carbonates and phosphates. A reduction of the alkali leading to a reduced power of absorption of carbonic acid occasions the phenomena of so-called acid intoxication, which is developed with striking intensity in herbivorous animals only. The determination of the degree of alkalinity is wholly unsatisfactory. Methods have been employed in which the amount of CO_2 is estimated by abstracting the gas *in vacuo*. These are accurate in so far as they indicate the amount of carbonic acid, but the alkalinity is not entirely due to alkalies in combination with carbonic acid, and in addition this acid

in small quantity at least would seem to enter into combination with calcium. The alkalimetric methods of determining the amount of alkalinity by titration, on the other hand, are unsatisfactory, as the entire quantity of alkaline bases are not concerned in the alkalinity, and notable differences result from the use of the entire blood or of the plasma. Upon the whole the gasimetric methods seem the most reliable in indicating the extent to which available alkaline bases have entered into combination with CO_2.

The Chemical Composition of the Serum.

Chemical analysis of the serum shows a special richness in chlorides and sodium, while the amount of potassium and albuminous bodies is small in comparison with that found in the corpuscles.

The specific gravity is normally about 1.025 to 1.030. In anæmic disease the average was found by Becquerel and Rodier to be 1.017. The color of the serum is due to a pigment of doubtful composition. Hammersten held this to be identical with bile pigment, but his view has not been generally accepted. Spectroscopically, however, the violet end of the spectroscope is darkened as is the case with the blood in jaundice, though less decidedly so. Krukenberg holds that the color is due to the same pigment as that occurring in fat, the *lipochrom*, and he found the same absorption bands with the spectroscope. The pigment of the serum is soluble in alcohol and ether and changes to a blue color when treated with iodine and sulphuric acid. The color is altered in conditions such as hæmoglobinæmia and jaundice, in which abnormal substances are superadded.

Among the albuminous substances serum-albumin and serum-globulin are always present, and the proportion of these varies but little in various forms of disease or in health under various circumstances. The total quantity of albumin according to Hammersten is somewhat more than 7.6 per cent. The relative proportion of serum-globulin to serum-albumin is as 1 to 1 or 1½. In diseases in which the albumin of the blood is destroyed the globulin increases in quantity, while serum-albumin decreases; and in elevations of blood pressure the serum-albumin escapes while the globulin is retained.

Of the saline constituents of the serum the sodium salts constitute by far the greatest part, these bases being in combination with phosphoric acid, carbonic acid, and sulphuric acid, and with chlorine as sodium chloride. Of the phosphates, neutral and acid phosphates are important.

The specific gravity and correspondingly the amount of water in the serum varies somewhat with disturbances of circulation and with

diseased conditions with which loss of water or retention of water is associated.

Changes in the Vital Properties of the Serum.

The blood serum, though in its chemical aspects merely an albuminous and saline liquid, is of such composition that it is capable of exercising most important vital properties. Investigations have shown that the serum under various conditions has the power to destroy living organisms or bacteria, to disintegrate red blood corpuscles, and to cause a general toxæmia. These properties have been recognized for a long time, and Landois, in particular, called attention in his studies on transfusion to the power possessed by the serum of destroying red corpuscles.

Among others, Buchner, Maragliano and Castellino, Daremberg, Rummo, and Carter have recently studied the changes which the serum undergoes in various conditions, particularly with reference to its toxic and globulicidal action. The serum of one animal is often intensely toxic for another, as is the serum of certain diseases for healthy animals. An increase of the globulicidal power (or the power to destroy blood corpuscles) has been found in various anæmic conditions and in a number of general diseases by Maragliano, Gilbert, and others. This is true of the action of the serum not only upon corpuscles of the lower animals, but also upon corpuscles of healthy human beings, and has been demonstrated by the decrease in number of the corpuscles in an animal after injection and also directly on a slide beneath the microscope. The essential nature of the changes or of the conditions which give to the serum this globulicidal power has not as yet been determined, though the amount of the saline matter contained in it would seem to be important and the substances most immediately concerned are probably albuminous in nature. The globulicidal property, however, is distinct from the toxicity of the serum, as the former may be removed by heating to certain degrees (55 to 60° C.), while the latter remains unaffected. To a large extent the toxicity is dependent upon the property of exciting coagulation in the smaller vessels of various organs.

Undoubtedly the conditions of the serum are primarily dependent upon alterations in the metabolism in various tissues or organs of the body more frequently than upon changes produced directly in the blood itself. In cases of infection the toxic properties are due to additions to the blood from the primary seat of disease in most instances, though occasionally no doubt the multiplication and growth of organisms within the blood itself may produce similar results *in loco*. The whole question, however, of toxicity and bactericidal power

of the serum is more appropriately considered in connection with the study of infections.

The Red Corpuscles.

Structure.—The red blood corpuscle, or erythrocyte, as it occurs in the adult is a rounded disc of elastic material, having a concavity or indentation upon each face, so that when viewed from either surface it presents a light-colored area representing the thinner part in the centre and when viewed from the edge shows a biscuit-shaped formation. The surface is smooth and the outline as a rule entirely circular; the color is light amber or yellowish. The corpuscles in the freshly drawn blood are extremely elastic, as may be seen when currents of the plasma move them about, and they tend to run together with the formation of columns resembling rolls of coin (*rouleaux*).

Histologically the corpuscles consist of an albuminous hæmoglobin-containing substance and a delicate stroma. There is no cell membrane. Foá holds that there is an outer layer, the hæmoglobin layer consisting of a fine network in the meshes of which are exceedingly fine granules which take the eosin stain with special avidity, while the inner part of the corpulscle consists of homogeneous protoplasm.

Size.—The size of the individual corpuscles varies greatly, the average, however, being from 7.5 to 8 μ. According to Hayem 12 per cent. are small in size (6 to 6.6 μ, *globules nains*), 75 per cent. middle sized (7–7.5 μ), and 12 per cent. large sized (8 to 9 μ, *globules géants*). In the new-born the size differs more markedly than in the adult; while striking variations occur in disease, as will be presently described.

Number.—The number of red corpuscles is estimated for given quantities of blood, no practical method as yet having been devised by which the amount of blood in the body can be determined clinically. The total number of red corpuscles therefore remains undetermined. The examinations of different investigators show the average number of red corpuscles per cubic millimetre in the healthy male to be about 5,000,000 and in the healthy female about 4,500,000. The individual figures, however, vary considerably from this. In the new-born nearly all investigators have found higher numbers, Hayem's figures being 6,262,000 as the maximum and 4,340,000 as the minimum. Other observers have found similar numbers. When the cord is tied before the cessation of the pulsations in the umbilical artery the number of corpuscles in the blood of the new-born is somewhat smaller than in cases in which tying the cord is delayed. Thus Hayem found on the average 5,087,000 in the former cases and 5,576,000 in the latter cases. Helot obtained similar results.

Various physiological and pathological conditions affect the number of the corpuscles, and more or less transitory variations and fluctuations are noticed in every individual from time to time. These variations will be considered more in detail under the head of polycythæmia and anæmia.

Volume.—The mass of the red corpuscles in the blood has recently been studied by a number of investigators, some of whom would give to this a greater significance than the determination of the actual number per cubic millimetre. The figures obtained by different investigators, however, have varied widely, and the methods thus far devised do not seem entirely satisfactory. Using the centrifuge Daland found the blood corpuscles to constitute 44 to 66 per cent. of the entire volume of the blood in fifty-five healthy men and 36 to 49 per cent. in eight healthy women. Gärtner found the proportions 46.5 to 48 per cent., and Herz estimated the normal volume at 40 to 50 per cent. The method of the Bleibtreu brothers has generally given smaller figures, Wendelstädt and Bleibtreu having found the proportions to vary from 25.15 to 41.1 per cent. In anæmic conditions the volume of corpuscles may become decidedly decreased, the last-named authors having found the percentage to vary from 9.52 to 49.1 per cent.

The *volume of the individual red corpuscle* may be approximately determined by the estimation of the number per cubic millimetre and the determination of the entire volume of corpuscles. The final result of course merely approximates the actual volume, since the figures are so great that slight errors would occasion considerable difference in the result. Welcker estimated the volume at 772 C. (C. being 1:10,000,000,000 c.mm.). Other observers have found larger numbers varying from that named up to 1,300 C. or more.

Chemical Composition.—The chemical composition of the red corpuscles has been frequently studied since the first investigation by C. Schmidt. The striking features are the small quantity of water and the large amount of albuminous substances. The most important constituent of the red corpuscles is the hæmoglobin, an albuminous substance containing iron. This constitutes nearly 14 per cent. of the weight of the blood as a whole, and 40.4 per cent. of the weight of the moist red corpuscles; and it makes up 95.5 per cent. of the organic matters of the red cells. Among the remaining organic constituents are other albumins (nucleoalbumin), lecithin, cholesterin. (For further consideration of *hæmoglobin*, see Spectroscopic Examination of the Blood.) The amount of iron in 1,000 gm. of blood cells has been variously estimated at 0.998 to 3.561 gm., according to the degree of inspissation or hydræmia of the blood. The amount of nitro-

gen was estimated by v. Jaksch, who found that the normal proportions vary from 4.93 to 6.38 per cent., the average being 5.52 per cent. This proportion varies greatly in anæmias. The total amount of dry residue has been found by Biernacki to be 29.28 to 29.99 per cent. in two healthy persons. Among the inorganic constituents sodium, potassium, chlorine, phosphoric acid, and iron are of particular interest. With increasing hydræmic conditions the amount of chlorine usually increases according to Biernacki. The potassium, phosphoric acid, and iron are moderately increased in the corpuscles in mild anæmias and reduced in severe anæmias, and usually the three are affected in about equal proportions. The same author found that the amount of hæmoglobin in the corpuscles is on an average greater in anæmic conditions than normally, this being no doubt dependent upon the varying quantity of water. The most variable constituent of the red corpuscle is water, the albuminous substances being relatively constant in amount.

Physiological Functions of the Red Corpuscles.

The important rôle of these structures is the absorption of oxygen in the lungs and its transportation to the tissues. The hæmoglobin is the active agent in this function, and as this substance forms by far the greatest part of the weight and bulk of the corpuscle the oxygen-carrying function would appear to be the most important property of the corpuscle.

Abnormalities of the Red Corpuscles.

Not unusually small forms or *microcytes* occur in severe anæmic affections, in various intoxications, after hemorrhage or extensive burns. These corpuscles may vary from 2 to 4 or 5 μ in diameter, and may be simple discs or biconcave formations. They were first observed by Masius and Vanlair. Undoubtedly they are in part merely young forms, as Hayem and Eichhorst have maintained; but it would appear that in part also they result from segmentation of the red corpuscles in consequence of degenerative processes, and the theory has been advanced by Litten that they are dependent upon the amount of saline matter in the blood and more recently by Biernacki that they are due to the discharge of plasma contained within the red corpuscle with a consequent decrease in their size. Their frequent occurrence after hemorrhage and in process of blood regeneration, however, warrants the belief that they are in most instances young forms and significant in the process of blood regeneration.

Corpuscles of excessive size (*macrocytes*, *megalocytes*) are observed in severe anæmias, notably in pernicious anæmia. They may vary in diameter from 9 to 12 or 14 μ and their protoplasm is often distinctly paler than that of the normal corpuscle, while there is frequently no evidence of biconcavity. Forms of this description are exceedingly common in the lymphoid marrow in conditions in which there is active hæmogenesis, and they may be looked upon as corpuscles which have found their way into the blood in an unfinished stage. It is likely, however, that in part they are degenerative in character.

In this connection, attention may be called to the observations of Herz, who has discovered alterations in the average size of the corpuscles in various diseases which he designates as acute or chronic swelling and which he looks upon as hydropic conditions.

Irregular red corpuscles were observed in the blood of leukæmia by Damon in 1864 and were subsequently studied by Quincke in pernicious anæmia and were regarded by this author as distinctive of this disease. He applied the name *poikilocyte*, while Ehrlich has more recently given them the title *schistocyte*, holding that the irregularity is the result of fragmentation. All forms of irregularity may be observed. Very commonly small beak-like elongations are noticed at some part of the periphery of the corpuscle or the latter may assume a club shape or may present undulating irregularity of contour. Occasionally the poikilocyte is angular in formation and it may be quite fragmental in appearance. The protoplasm is frequently very poor in hæmoglobin, which seems to be present only about the periphery or in the projecting portions, while the disc in general is almost colorless. Exceedingly small forms, sometimes of rod-like shape, have been described by Hayem as *pseudobacilli*. They have doubtless often been mistaken for bacteria or monadines, on account of their small size and their active movements, spontaneous or due to movements of the plasma.

The nature of these changes of form constituting poikilocytosis is as yet undecided, though it is highly probable that they are distinctly degenerative. This view is largely confirmed by the observations of Maragliano and Castellino, who found that the blood corpuscles under various conditions outside the body undergo degenerative or necrobiotic changes, leading to the formation of *endoglobular changes*, as well as to alterations of the entire corpuscle, *total necrosis*, presenting itself in the form of irregularity in outline. This irregularity is due according to these observers to the active amœboid movements of the degenerating cell. At the same time portions of the corpuscle may become broken off and circulate as small fragmental cells.

While the views of Maragliano and Castellino are based upon somewhat crude experiments, they undoubtedly point in the direction of the truth, and nearly all authorities agree that poikilocytosis is an expression of advanced degeneration. It was formerly held by some that the changes in form are wholly artifacts. This is completely disproved by all recent observations, and though it is entirely true that post-mortem changes in the corpuscles outside the body may lead to poikilocytic formations, there can be no doubt that these changes are actually present in the blood in severe anæmias during life. Poikilocytosis is in no wise a certain indication of progressive pernicious anæmia, as Quincke held, but occurs in advanced anæmia of any kind.

Amœboid movements of the red corpuscles sometimes present themselves in cases of severe anæmia. These were first seen by Friedreich in leukæmia and have subsequently been studied in pernicious anæmia and other conditions. They may be slow and undulating or exceedingly active. The active movements of the pseudo-bacilli of Hayem have been alluded to; in part the latter movements are molecular in character; in part, however, they are the result of amœboid activity of the corpuscle itself. The slower movements of the large corpuscles (normal, macrocytes, or poikilocytes) are clearly amœboid, and may cause a progression of the corpuscle across the field of the microscope. The movements of the corpuscles due to currents of plasma must not be mistaken for amœboid movements.

Fig. 26.—Nucleated Red Corpuscles, showing Karyokinesis.

Nucleated red corpuscles occur in the blood in the course of anæmic disease as in the fœtal blood. They may be either small forms, the size of the normal red corpuscle, or even much smaller (*normoblasts* and *microblasts*), or large forms much greater in size than the normal corpuscle (*megaloblasts*). The smaller forms usually present themselves first and in the more moderate grades of anæmia. In the severe cases, as in pernicious anæmia, leukæmia, cancerous cachexia, and like conditions, the megaloblasts may be conspicuous. Nucleated red corpuscles are seen with especial frequency in childhood, at which period they may occur in quite moderate anæmias. The nuclei may be simply rounded masses having a dense chromatic network,

but sometimes double or triple forms (*clover-leaf nuclei*) are seen and actual karyokinetic figures (Fig. 26) are not rarely observed (Luzet, v. Noorden, Troje, Askanazy). Nucleated corpuscles are undoubtedly the expression of active hæmogenesis, the smaller forms being particularly significant. Occasionally these appear in separate crops (*blood crises*, v. Noorden) followed by increase in the number of red corpuscles in the blood. The larger forms, according to Ehrlich, are expressions of imperfectly conducted hæmogenesis, but this view it seems to me cannot be well maintained. On the contrary, they would appear to be the expression of unusual demands upon the hæmogenetic function, in which the large as well as the small forms escape from the bone marrow before the development of the corpuscles has been completed. Sometimes the large nucleated forms are very irregular in shape (*poikiloblasts*).

Degenerations of the Red Corpuscles.

In the course of certain intense anæmias, and particularly in cases of poisoning by hæmolytic agents, certain forms of red corpuscles appear in the blood which are appropriately termed *shadow corpuscles* (Ponfick). They are simply discs presenting the appearance of red corpuscles which have almost or quite lost their coloring matter, leaving only the stroma or colorless substance, and in which the circumference of the corpuscle may alone be visible. The number of these is rarely great, although sometimes they are present in quite considerable proportions. They may be observed in the freshly drawn blood, but are prone to develop after the blood has been removed from the body, and care is therefore necessary to obviate this source of error.

In other cases the protoplasm of the corpuscle may contain vacuoles or apparent fenestrations, or again there may be pigmented areas standing out prominently from the remaining substance. Such alterations are rarely met with in the blood of anæmic disease, but have been frequently produced by the administration of hæmolytic poisons and by subjecting the blood after its removal from the body to conditions which occasion necrotic changes. Ehrlich called attention to a form of degeneration which he designated as hæmoglobinæmic disintegration, and in which the corpuscles present in their protoplasm small globules having the appearance of concentrated droplets of hæmoglobin. Such changes have been found in the corpuscles in poisoning by phenylhydrazin and by other hæmolytic substances. Other degenerative conditions manifesting themselves by a granular character of the protoplasm have been noted by Foá, and my own

observations have disclosed the presence in advanced anæmias, either chlorotic or of other kinds, of corpuscles containing sometimes indefinite granular matter, at other times definite round globules or granules of high refraction and distinct pinkish color, which have suggested the idea of separate masses of hæmoglobin. My first impression on seeing these appearances was that they were artifacts, but later and careful examinations convinced me that they are really alterations in the structure of the red corpuscles occurring during life.

A most important evidence of alteration of the protoplasm of the red corpuscles is discoverable in staining the blood. Gabritchewski showed that the living red corpuscle is entirely *achromatophile*, refusing all forms of stains, and I am able to substantiate this so far as my attempts to produce intravascular staining by the administration of methyl blue and other aniline dyes are concerned. When the corpuscles are rapidly fixed by heat or chemical substances they become *monochromatophile*, so that from the mixture of colors (such as eosin and hæmatoxylin) only one of these colors (the acid stain) is received. In certain conditions the red corpuscles are found to be *polychromatophile*, so that instead of receiving one color the tinge received is a mixture of the several colors employed. After using hæmatoxylin or methyl blue and eosin we observe that such corpuscles present a violet appearance instead of a normal pink or red. Ehrlich believed that this peculiarity was due to coagulation necrosis of the cytoplasm and pointed to its occurrence in severe anæmias. Gabritchewski, Askanazy, and Schumann, however, found this peculiarity mainly in the younger corpuscles and often in nucleated corpuscles showing signs of karyokinesis. Askanazy saw it in nearly all of the nucleated corpuscles from the bone marrow or freshly resected ribs, and in the marrow of pernicious anæmia in one of my cases the same condition obtained. It would seem, therefore, that the view of Ehrlich and that of Maragliano and Castellino, who demonstrated the frequent occurrence of this change in the artificially degenerated corpuscles produced in their experiments, ought not to be too readily accepted. It is possible, however, that the same peculiarity regarding stains obtains in the undeveloped youthful corpuscles and also in the older forms which have become partly degenerate; and the view accepted by certain writers, and first promulgated by F. P. Henry, that the alterations in the appearance of the red corpuscles in various anæmic states represent a retrograde metamorphosis to more youthful conditions or to the type of corpuscles seen in the lower animals (reptilian) is interesting in this connection.

Isotonicity of the Red Corpuscles.

Donders, and subsequently Hamburger, v. Limbeck, and others have studied the resistance of the red corpuscles to various solutions to determine their osmotic relations. All forms of cells have a certain osmotic potentiality (*turgor*, de Vries), in consequence of which they give up their constituent elements when the surrounding liquids have certain relations. In the case of blood it is found that distilled water causes a rapid removal of the hæmoglobin and doubtless other constituents from the corpuscles. Within the living body this is prevented by the constitution of the plasma, and outside the body saline solutions exercise the same preservative influence. When these solutions are reduced in strength there is found a point at which the osmotic movements from the corpuscle begin to manifest themselves by solution of the hæmoglobin in the surrounding liquid. The solution just sufficiently strong to prevent this is spoken of as an *isotonic* solution, and the *isotonicity* of the corpuscle is measured by the strength of the saline solution. This varies with different substances according to their molecular weight. Solutions of greater concentration are *hypertonic;* those of lower concentration *hypotonic*. The plasma is always hypertonic, though the degree varies somewhat in different cases. It is likely that vital forces are concerned in these phenomena, as well as the mere physical osmotic relations. This question, however, is unsettled.

In normal persons the isotonicity of the erythrocytes is generally about 0.46 per cent. NaCl—that is, a 0.46-per-cent. solution of common salt preserves the corpuscles. In disease this varies somewhat. The subject has been investigated quite elaborately by v. Limbeck, but as yet no definite results have been obtained. My own experiments in this direction have given very divergent results. In two cases of pernicious anæmia I found the isotonicity 0.52 and 0.6, but in other cases it was normal, while in general diseases marked by anæmia (including carcinoma, cirrhosis of the liver, renal affections, and tuberculosis) the variations were trivial. The mechanical manipulations in the examination exercised a decided influence, and congestion of the finger or exposure of the finger to a freezing mixture always caused diminution of the isotonic strength of the corpuscles.

The Leucocytes.

The white corpuscles are rounded or spherical cells generally presenting a slightly granular appearance when examined in the fresh blood. Their size varies from that of a red corpuscle to several

times the diameter of the latter. On the addition of weak acetic acid the protoplasm is cleared and the nucleus (single, polymorphous, or multiple) appears to view. The white corpuscles are identical with the lymph corpuscles; their function remains obscure. There is

FIG. 27.—Normal and Pathological Red and White Corpuscles. *a*, Normal red corpuscles; *b*, nucleated red corpuscles; *c*, lymphocytes; *d*, large mononuclear; *c'*, transitional forms between *c* and *d*; *e*, transitional forms; *e'*, transitional neutrophiles; *f*, polymorphous Forms; *g*, eosinophiles; *h*, myelocytes.

little doubt but that they bear important relations to the processes of metabolism.

Origin (see also Blood Formation).—The source of the white corpuscles is undoubtedly the lymphatic glands as well as the other lymphoid structures, including the bone marrow, the spleen, and the gastro-intestinal lymph follicles. The earliest or youngest leucocytes are small mononuclear cells with comparatively little protoplasm. Subsequent changes occur in these leucocytes and give rise to some at least of the other forms met with in the blood. The place or the manner in which these changes occur has not as yet been determined. It is likely, however, that transformations occur in the spleen, and

notably in the bone marrow, and it is probably that the specific functional activity of these structures is important in determining the processes of development in the circulating leucocytes.

Ehrlich and his pupils at first maintained, as had Virchow previously, that certain large leucocytes originated primarily in the spleen. In the light of recent investigations, however, it is likely that the cells coming originally from the spleen, like those of the lymphatic glands or other lymphoid structures, are small mononuclear forms (lymphocytes). In the spleen and in the glands they originate within the Malpighian bodies or follicles, the so-called *germ-centres* of Flemming.

Structure and Varieties. — The classifications which have been offered of the leucocytes have been very numerous and various, and it is impossible even at the present day to offer a scientific and in all respects satisfactory scheme. Virchow first divided the white cells into the small mononuclear forms which he believed to originate from the lymphatic glands, and large mononuclear forms supposed to be derived from the spleen. Increase of the former he designated lymphæmia; of the latter, splenæmia.

Subsequently, however, other classifications of a more comprehensive character have been introduced. That in vogue at the present time originated with Ehrlich and his pupils, notably Einhorn. Ehrlich classifies the leucocytes in two ways: (1) according to the size and shape of the cell and the appearance of the nucleus; and (2) according to the granulations within the cells. The forms based upon the morphological characters are as follows:

1. *Small Mononuclear Leucocytes or Lymphocytes.*—These are generally smaller than the red corpuscle or about the same size, are circular in outline, and contain a relatively large nucleus, the protoplasm being scarcely visible in some cases or forming a very thin band surrounding the nucleus. The latter is usually quite rich in chromatin and therefore stains darkly with the nuclear stains. In certain instances cells which must be included among the lymphocytes are considerably greater in size than those commonly observed, and they may be quite indistinguishable from the next form, the large mononuclear. In these cases a distinction may possibly be found in the greater intensity with which the nucleus stains in true lymphocytes, but this distinction is by no means possible in all cases. A sharp dividing line cannot be drawn between the typical lymphocyte and the large mononuclear forms. The gradual transition is seen in the diagram, Fig. 27, *c*, *c'*, *d*. Reference will be made in the section on leukæmia to the abundance, in some cases of acute lymphatic leukæmia, of cells of the kind here alluded to.

The protoplasm of the lymphocytes normally contains no granular matter discoverable by any of our methods. It may be slightly tinged but is apparently homogeneous.

In certain instances, however, small white corpuscles, which must from their morphological characters be ranked as lymphocytes, present granulations. Thus I have seen them not infrequently filled with neutrophilic granules or oxyphilic granulations, and in leukæmic blood I have found mastzellen granulations.

The relative proportions of the different forms of leucocytes will be given below.

2. *Large Mononuclear Leucocytes.*—These forms are considerably larger than the lymphocytes, being generally two or three times the diameter of the red corpuscle. Frequently they are somewhat oval in outline. The nucleus is larger than that of the lymphocyte and the chromatin is considerably less compact, so that the nucleus is pale in comparison with that of the lymphocytes in blood stained with basic stains. The protoplasm is generally free of granulations and usually stains very slightly with eosin or other stains. Eosinophilic, basophilic, or even neutrophilic granulations may occur, but in the great majority of cases the protoplasm is clear.

3. *Transitional Forms.*—These are practically indistinguishable from the large mononuclear forms, excepting that the nucleus in the transitional forms is indented and often presents a distinct horseshoe shape. The name transitional was applied by Ehrlich with the idea that these forms represent intermediate stages between the mononuclear forms and the polymorphous leucocytes. The early occurrence of neutrophile granulations in the protoplasm of the transitional corpuscles in certain conditions and their morphology alone seem to warrant this view. The nucleus is poor in chromatin as in the mononuclear forms, and the protoplasm is free of granules. Very rarely Einhorn found neutrophilic granulations in these cells in the normal blood, and others have established the same fact. Eosinophile granulations occur in a small proportion of these cells.

4. *Polymorphous Leucocytes; Polynuclear Leucocytes; Neutrophiles.*—These, which make up the greatest part of the leucocytes of the normal blood, are somewhat smaller than the large mononuclear elements and are characterized by a polymorphous nucleus which is usually rich in chromatin, and has a decidedly irregular shape. Most frequently it resembles the letter S; in other cases the letters U, V, Z, etc. Complete fragmentation sometimes occurs and the cell then presents itself as a truly polynuclear leucocyte, but in most instances the multiple character of the nucleus is only apparent, fine strands of chromatin uniting the different portions but being them-

selves obscured. The term polymorphous (Ehrlich) is for these reasons more appropriate than the older name polynuclear. The nucleus is deeply stained with basic colors but the intensity varies greatly. In some instances, particularly in leukæmia, I have been struck by the fact that the chromatin of some of the polymorphous nuclei was exceedingly scanty, while others stained intensely. The protoplasm almost invariably contains fine granules, filling up the entire substance of the cell and showing a particular affinity for Ehrlich's neutral stains. Occasionally it is impossible to demonstrate granules of any kind in these cells, and in some instances the granules show quite as much affinity for eosin or other acid stains as for the neutral mixtures. True eosinophile granules, however, may be found in polynuclear cells of the same general appearance as those in which neutrophile granulations are customarily met with.

The nature of the polymorphous cells and their origin have occasioned much discussion, and they have been variously regarded as independent formations or as terminal stages in the process of development or degeneration of the other leucocytes. It would seem from recent investigations that they are in all probability the terminal forms in the cycle of maturation of leucocytes, that in a sense they are "ripe" or "over-ripe" formations (Uskow); and that the final transformation occurs in the bone marrow or in other parts of the lymphatic apparatus rather than in the blood itself.

Myelocytes (*Markzellen*).—The foregoing are the morphological forms of leucocytes met with in the normal blood. In disease a variety not as yet mentioned has been described and has excited very great interest. These are the so-called myelocytes or markzellen. These forms were first recognized by Mosler, but subsequently were described by Cornil (*cellules médullaires*) and Robin (*médullocelles*). Ehrlich attributed great significance to the same forms in the diagnosis of leukæmia and recently they have been studied by H. F. Müller, who has pointed out the similarity or identity of the large cells described by different authors and their relations with the cells of the marrow. According to Ehrlich the myelocyte is identical with the large mononuclear cells in gross morphology, and differ only in containing neutrophilic granules. In these features they are identical with certain cells found in the bone marrow, and Ehrlich's pupil Uthemann named them definitely the *myelocytes*. These cells are large bodies from three or four to six or seven times the diameter of red corpuscles, having an extremely pale nucleus, sometimes with an irregular outline but more usually rounded or oval and lying in the centre or often towards one side of the cell. The protoplasm of the myelocyte usually contains granules staining with the neutral

mixtures of Ehrlich, but in certain cases they are oxyphilic or eosinophilic. It is the myelocytes in particular, among all of the leucocytes, that are devoid of amœboid movement. The description by Ehrlich was less distinctive. According to this author, as has been stated, the myelocytes are indistinguishable from the large mononuclear or transitional forms, excepting for the presence of the neutrophilic granules. In some instances undoubtedly Ehrlich's description applies, but the typical myelocyte differs from the large mononuclear or transitional form in the much greater size of the corpuscle and in the unusual pallor of the nucleus. Undoubtedly these leucocytes may be distinguished by their morphology alone in many instances, but the smaller forms approach so nearly the ordinary mononuclear elements that differential stains are necessary to distinguish the nature of the individual corpuscles, and even after this test doubt may exist as to the proper classification.

Undoubtedly the myelocytes or markzellen originate in the bone marrow and are identical with the cells found in that situation. It does not seem proper, however, to distinguish them entirely from the ordinary leucocytes; but it would appear rather that they represent a certain stage in the cycle of development of the leucocytes which is ordinarily conducted within the bone marrow, and that exceptionally they escape into the circulating blood when the conditions of the marrow lead to their extrusion in an unfinished stage.

The Granulations of the Leucocytes.

The granulations of the blood were first studied by Ehrlich in a thoroughly scientific manner, the method of "color-analysis" introduced by this author furnishing the means by which his discoveries were made. Previous writers had called attention to the occurrence of granulations, either fine or coarse, but little significance was attached to these. Ehrlich was able to distinguish in all seven forms of granules in the leucocytes, five of these occurring in human blood. The classification of these granulations is based upon certain peculiarities of the stains employed. Ehrlich distinguishes acid and basic stains, the former being such as contain the staining element in the acidulous part of the compound, the latter those in which the base forms the stain. For example, the picrate of ammonium represents a typical acid stain in that the picric acid of the salt is the active coloring agent. Certain mixtures of the acid and basic stains may be made in such manner that a neutral stain results. The five varieties of granules have been distinguished by using the Greek letters α to ε.

α-Granulations, eosinophilic granules, oxyphilic granules. These occur in the body of the white corpuscles as very coarse granular bodies presenting in the unstained blood somewhat the appearance of minute fat droplets for which they were formerly mistaken. They are highly refractive and when small may appear as black points. The nature of these bodies was principally determined by Ehrlich, and he definitely disproved the older view that they were fatty in nature. Certain authors who have succeeded in staining them black with osmic acid still assert that they are fatty bodies, but, as Wertheim and Müller maintain, this test is insufficient; and the elaborate investigations of Ehrlich, in which the granules in question were found to be unaffected by prolonged exposure to ether and other reagents, are definite and conclusive. Notwithstanding Ehrlich's view that they are non-albuminous, Weiss, Posner, Kossel, and others have shown that they are albuminous bodies, while the studies of Barker and Przewoski make it seem likely that they contain iron.

The oxyphilic granules distinguish themselves by their peculiar affinity for acid stains and in particular for eosin (therefore the name eosinophiles). They vary in coarseness and in amount in different cases. In some instances I have found eosinophile granules in a considerable proportion of the leucocytes of the blood, but so few in number in each cell that many of the leucocytes contained only a few granules. As a rule the cell is densely packed with them. They occur for the most part in large cells having polymorphous nuclei, resembling those of the ordinary neutrophilic leucocyte, though as a rule the nucleus is less rich in chromatin. Less frequently they occur in lymphocytes, in the ordinary mononuclear forms, or in the myelocytes. The number of cells presenting eosinophile granules varies considerably in health. They are usually more abundant in the new-born than in adults. In the latter they vary from 0.67 to 11 per cent. (Zappert), but as a rule not above two to four per cent. of the entire number of leucocytes present this character. Ehrlich held that the increase of eosinophile cells is an indication of a chronic disturbance of hæmogenesis, and particularly of implication of the bone marrow as in myelogenic leukæmia. This view has been abandoned. The eosinophile granulations may be less abundant in leukæmia than in the normal blood; and a decided increase is frequently observed in asthma and emphysema, in certain skin diseases, and occasionally in a great variety of affections. Such an increase of oxyphilic cells (sometimes termed *eosinophilia*) has, however, no definite significance; and the attempt of Neusser to connect this condition with disturbance of the sympathetic nervous system is

fanciful. A great decrease in the eosinophilic corpuscles is observed in croupous pneumonia and in certain cases of tuberculosis.

The origin of these granules is still exceedingly doubtful, and Ehrlich's view, based upon their abundance in the bone marrow, that they originate entirely in the bone marrow, is no longer entertained. It is likely that they may have a local origin in various parts of the body and in particular in the skin, as the abundant occurrence of these cells in certain skin diseases, locally and in the blood, and their frequency in some instances of suppurative inflammation would indicate. As to their nature, but little has been determined. The theory deserves consideration that they are albuminous precipitates resulting from the absorption of water by the protoplasm of the cell. It is unlikely that they are specific products of the cell itself (*Product einer specifisch-secretorischen Thätigkeit*, Ehrlich). It is likely on the other hand that they are evidence of the ripening of the leucocyte, or represent a phase in the cycle of maturation.

β-Granulations are fine granules which stain with acid and also with basic stains. The term *amphophilic granules* is therefore applicable. They have been found particularly in the bone marrow but have no special significance.

γ-Granulations, *Mastzellen-granulationen*, are intensely basophilic and rather coarse granules, occurring for the most part in mononuclear cells which are often densely filled with the granules in question. Canon found these in the normal blood in a considerable proportion of cases in children, but most investigators have found them only in leukæmia. They are probably closely related to or identical with the plasma cells of Waldeyer.

δ-Granulations are fine basophilic granules occurring in large mononuclear cells. Usually they are faintly stained and exceedingly fine. I have seen them in the blood of normal persons in very small numbers. No special significance can be attributed to these forms.

ε-Granulations or *neutrophilic granules*. These are the most important and abundant of all of the granules. They occur as fine points filling up the entire protoplasm of the polymorphous cells, in which they occur in normal blood, giving to these cells in the unstained specimen a slight opacity or granular character. In the stained blood they receive the neutral mixtures of Ehrlich with special affinity. Occasionally, however, I have found them decidedly oxyphilic, receiving eosin and acid fuchsin very readily. Sometimes the cell may contain relatively few neutrophilic granules, though the rule is, as stated, that the cell is densely filled with them. In normal blood the neutrophilic granules occur almost exclusively, or exclusively in the polymorphous leucocytes, but in pathological con-

ditions they may be found in the large mononuclear cells or myelocytes and sometimes in small cells which from their morphology must be classed as lymphocytes.

The number of cells presenting neutrophilic granulations varies somewhat in health and very widely in disease. They constitute about 60 to 75 per cent. of the leucocytes of the normal blood; but in certain cases of inflammatory leucocytosis fully 90 or 95 per cent. may be of this type. In one of my cases the proportion was 98.5 per cent. The cells of exudative inflammations and of pus are usually all polymorphous and neutrophilic; exceptionally oxyphilic or eosinophilic granules are abundant. This has been noted in certain skin diseases and in gonorrhœal pus, as well as in the leucocytes of the sputum in asthma and those in the fæces in certain diarrhœas. The increase of neutrophilic cells in leukæmia is always striking. In this case a great proportion of the cells, no matter to which morphological group they belong, may present neutrophilic granules, this fact distinguishing the blood from that of inflammatory leucocytosis in which only the polymorphous neutrophilic cells occur.

The Nature of the Granulations.—These peculiar bodies within the protoplasm of the leucocytes were well known to the older writers, who sometimes spoke of the fine granules and coarse granulations. Little attention, however, was given to them until Ehrlich had introduced his method of coloring based upon the reaction of the different granules to definite mixtures of aniline or other coloring agents.

The nature of the granules, however, still remains obscure despite the abundant observations of a great number of investigators. Ehrlich was inclined to look upon them as definite products of the protoplasmic activity of the leucocytes and therefore gave them the title *specific granules.* Subsequent authors, however, have inclined to view them as evidences either of degenerative changes or of progressive changes leading to a "ripe" or "over-ripe" condition. In this connection the eosinophile granules, being the largest and most conspicuous, have been particularly interesting. A point which seemed to favor the view of Ehrlich that they are evidences of a specific secretory power (*specifisch-secretorische Thätigkeit*) was his observation that one form only occurs in a given cell. This observation, however, has not been confirmed by all observers, and Arnold in particular has found certain cells in the bone marrow which presented more than one form of granulations.

They undoubtedly represent a phase in the development of the leucocytes, as the occurrence of neutrophile granules in a large proportion of all of the leucocytes of the normal blood, and of eosinophile granulations in a smaller proportion would indicate. Moreover, their

presence in the cells in which the most decided functional activity (amœboid movement, migration) is known to occur, justifies the belief that they are in some manner related with the functional activity of the white corpuscles. Whether this is dependent upon a secretory function or whether it is in some way the result of metabolic interchange between the leucocyte and its surrroundings is a matter upon which no dogmatism is justified. It seems certain that the granulations are in no sense evidence of degeneration, as in the first place their abundance in the blood and in the second place the absence of evidence of nuclear degeneration in these cells would indicate. The view, recently expressed, that they are in a manner related with the absorption of liquid from the surrounding media is attractive, but rests entirely upon speculation. There seems to be undoubtedly a close relation of the different forms of granules, since a number of observers have found that they occasionally react as well to acid as to neutral stains. I am able to confirm this from my own observations, and indeed have found that basic stains may answer in certain cases for neutral or even acid granulations. It must be remembered that the distinctions established by Ehrlich rested upon the *special* affinity for certain stains rather than upon an exclusive and narrow affinity; but even in this case, or perhaps because of this fact, it may be held that the granules are only slight variations of a common substance and that they may all be expressions in greater or less intensity of a similar process. The exact chemical composition of the granules has not as yet been determined accurately. They are undoubtedly albuminous in nature, as Weiss and others have shown, and in all probability the eosinophilic contain a certain proportion of iron.

The Proportions of the Several Forms.

The relative proportions of the different forms of leucocytes have been estimated in health and in a great variety of diseases and often furnish important indications of the nature of disease processes. Einhorn, working under Ehrlich's direction, found the lymphocytes to constitute 25 per cent. of the total number of leucocytes, the polymorphous cells 65 to 70 per cent., and the transitional and eosinophile forms together 5 to 10 per cent. These figures correspond quite well with those obtained by other investigators. The large mononuclear and transitional forms taken by themselves usually constitute from 3 or 4 to 5 or 6 per cent., and the eosinophile corpuscles on an average not above 3 to 5 per cent., although Zappert in his investigations found as many as 11 per cent. in healthy persons.

The proportions vary considerably in disease and also in the same

person at different times. In childhood or infancy the younger forms or lymphocytes are relatively much more abundant than the older or polymorphous forms. The percentages vary from 50 to 66 for the lymphocytes and 28 to 40 for the polymorphous variety (Rieder and Gundobin). The large mononuclear forms like the lymphocytes are rather more abundant in early life and the eosinophile cells may be quite numerous. These conditions remain, according to Gundobin, until about the third year, when the proportions become those characteristic of adult life.

Weiss has pointed out that it is deceptive to state the percentage proportions of the different forms, since the increase of one form in particular would cause a relative decrease of another variety, though the latter might be present in its normal proportions. It would, therefore, be advisable in all cases to state the exact numbers per cubic millimetre of each of the forms rather than the relative number. In this way the separate increase of one or another form would be indicated rather than an apparent decrease of all of the forms with relative increase of one.

The myelocytes have occasionally been found in the blood of apparently normal persons; but this is very exceptional. They are met with in a variety of diseases, however, and have lost some of their importance as an indication of leukæmia (see section on Leukæmia).

Karyokinesis.

Karyokinetic changes were first observed in the leucocytes of the circulating blood by Flemming. Since his publication they have been demonstrated by a number of authors. The subject, however, will be more fully considered in the article on leukæmia.

Amœboid Movements.

One of the most conspicuous and doubtless important peculiarities of the leucocytes is their amœboid activity. Attention was first called to this by Dutrochet in 1824 and by Wharton Jones in 1846. Subsequently the capability for active movements of the leucocytes figured largely in Cohnheim's teaching of the pathology of inflammation, and very recently the theory of phagocytosis of Metchnikoff has been largely based upon the amœboid activities of the leucocytes. All forms of the leucocytes do not possess this power. It is particularly characteristic of the polymorphous elements, while the lymphocytes may show almost no activity or may be entirely quiescent and the large mononuclear cells and the myelocytes are usually completely

void of movement. In leukæmia, in which the mononuclear elements are particularly abundant, the absence of amœboid movements is always striking, and certain authors were disposed to attribute this to degenerative changes and to look upon leukæmia as a disease dependent upon degenerate conditions in the leucocytes themselves. This was the view of Biesiadecki, who first noted the absence of amœboid movements in leukæmia, and later of Cavafy and others. At the present time, however, it is recognized that the sluggishness of the leucocytes in leukæmia is without significance, since the same forms of cells in the normal blood are equally devoid of movements. In the processes of chemotaxis and inflammation in which the active amœboid movements of the leucocytes are concerned it is always the polymorphous elements which are attracted, and in the diapedesis through the walls of the vessels it is the same forms that escape from the vascular channels.

Chemical Characters.

The chemistry of the leucocytes has been somewhat difficult to determine since the quantity obtainable from the blood is insufficient for analysis. The studies thus far recorded have therefore been based almost wholly upon analyses of pus cells or of the lymph cells of lymphoid tissues like the thymus gland. Certain investigations have been made in cases of leukæmia, but the results as a rule are unreliable. Among the organic constituents of the leucocytes a compound known as nucleohiston and lecithin are the more important, while an analysis of the ash shows a high proportion of phosphoric acid or phosphates, these no doubt dependent upon the considerable percentage of nuclein contained in the nuclei of the corpuscles. The recent chemical studies of Lilienfeld, Kossel, and others have shown the principal organic substances of the pus and lymph cells to be the albuminous bodies leuconuclein and histon, lecithin and cholesterin. These are designated as the primary bodies of the leucocytes in contradistinction to such as occur occasionally and only in certain cells which they designate as secondary bodies. Among the latter are glycogen, protagon, and fats. The dry residue of the leucocytes was found on the average to be 11.49 per cent. by Lilienfeld. Of this residue the important constituent was the leuconuclein. The latter is a combination of the phosphorus-containing nucleinic acid with albumin, making by their conjunction a form of nucleoalbumin, called leuconuclein. It occurs according to Kossel in the nuclei of the nucleated red corpuscles as also in the lymph cells in combination with another albuminous body, resembling the albumoses (*histon*), the com-

pound being the so-called *nucleohiston*. Studies made by the method of color analysis show that the leuconuclein is oxyphilic in reaction, while the histon is basophilic.

Degenerations of the White Corpuscles.

No very definite facts have been learned regarding the degeneration of leucocytes. Attention has already been called to the view tertained by Biesiadecki and others that the apparent want of amœboid movements in the leucocytes in leukæmia is an evidence of degeneration. This view cannot now be maintained. Others have looked upon the granulations of Ehrlich or some of them as degenerative in nature, but such a view lacks confirmation. Practically nothing is positively known regarding the significance of these granules.

Recently attention has been fixed upon the nuclei of the white corpuscles, and various conditions have been noticed which certainly warrant the belief that processes of disintegration or degeneration may be represented by these.

Neusser has called attention to certain granular formations found in the protoplasm of the leucocytes surrounding the nucleus. These occur with especial frequency in the mononuclear leucocytes and are distinguished by their affinity for the basic element (the methyl green) in Ehrlich's triacid mixture. Such formations were found in cases of gout and also in other conditions, such as tuberculosis, leukæmia, and diabetes, in which a lithæmic condition in its widest sense may be assumed to exist. Neusser believes the granules to be substances allied to nucleoalbumin and regards their appearance as significant of degeneration or disintegration of the nuclei leading to uric-acid formation. The nature of these granules is by no means as easily explained as Neusser believes, but is as yet undetermined. They have been found in white blood cells under conditions in which no degenerations could be assumed to exist.

Reference is made in the pathology of leukæmia to the occurrence of leucocytes, in which the chromatin network of the nuclei is excessively scanty and irregular. The outline of the nuclei may be shadowy or broken and light areas or even vacuolation may be seen. These conditions strongly suggest degenerative changes, as Gumprecht has maintained, but their significance must be further investigated.

Undoubtedly degeneration or destruction of the leucocytes, and in particular of their nuclei, occurs in some part of the circulation or in the tissues. Recent studies show conclusively that the xanthin

bases and uric acid are derived from such destruction, but whether the granulations of Neusser or the nuclear irregularity of Gumprecht and others may be taken to be demonstrable evidences of such processes, remains to be proved.

Salomon, Gabritchewsky, Lieveriata, and others have demonstrated the presence of glycogen or allied substances in the leucocytes by staining with iodine. Whether this is normal or degenerative is doubtful.

In examinations of the fresh blood or of specimens fixed upon cover glasses after Ehrlich's method, it frequently happens that "broken cells" are observed. These are leucocytes which have become fractured so that the protoplasm, the granules, and even the nucleus may be fragmented and somewhat spread out. The exact significance of these conditions is not determined, but it is evident that the leucocytes in question have in some way lost their coheiveness. The eosinophile leucocytes show this phenomenon most strikingly.

The Blood Plaques.

The blood plaques, first recognized by Max Schulze, Kölliker, Riess, Ranvier, and Hayem, were studied with particular care by Bizzozero in 1882. The same year Osler published interesting observations on the same subject.

Structure.—They appear as circular discs somewhat resembling the red corpuscle, though much smaller, paler, and without the characteristic biconcavity of the erythrocyte. The size varies somewhat but is rarely above 3 μ and often considerably less. The placques are specially characterized by a certain viscidity, which causes them to adhere to the leucocytes or red corpuscles or more frequently to become agglutinated in small clusters. Their color is very faint and of a somewhat yellowish hue. The protoplasm is entirely clear and homogeneous or at times somewhat granular.

Number.—The number of blood plaques is difficult to determine on account of their extreme liability to disintegration. It has been variously estimated at 180,000 to 250,000 (Fusari), 200,000 to 300,000 (Afanassiew), and 500,000 (Pruss).

They are readily stained with aniline dyes and are amphophilic in color affinity, taking up either acid or basic stains. Methyl blue or violet stains them quite well.

Nature.—The nature and origin of these bodies have occasioned much difference of opinion and are still undetermined. Bizzozero first described them as a third corpuscular element, while Hayem, noting their abundance in certain anæmic diseases during the stage of regen-

eration, thought them important in the development of red corpuscles and applied the term *hæmatoblasts*, by which French writers still designate them. Löwit held that the blood plaques do not occur in the living blood and that they are artifacts resulting from precipitation of globulin from the plasma or from degeneration of the leucocytes. Very recently Lilienfeld has taken much the same view, holding that the plaques are derivatives of the nuclei of leucocytes. He does not, however, agree with Löwit regarding the chemical nature of the plaque. His own experiments would seem to indicate a resemblance in composition of the blood plaques and the nuclei of the leucocytes, both containing a combination of albumin and nuclein. Notwithstanding these views it is most likely that the plaques occur as formed elements of normal blood. Indeed Laker and Bizzozero claim to have seen them in the circulating blood of certain lower animals during life.

Functions.—But little is known regarding the functions of these bodies. They play an important rôle in the process of thrombosis, particularly in the formation of white thrombi; but beyond this nothing can be said of them. They are increased in numbers in certain non-febrile anæmic conditions, especially during the period of regeneration of the blood; also after hemorrhages, in lukæmia, and occasionally in other conditions. They are reduced in number in febrile affections.

Foreign Matters in the Blood.

Various particulate elements may occur in the blood under pathological conditions, and may have great clinical or pathological significance. *Pigment matter* has long been known to occur in malaria and other conditions in which destruction of the red corpuscles is taking place. The pigment may be entirely the result of degeneration of the erythrocytes or may arise in other ways. The condition of the blood is termed *melanæmia* (see below). *Fatty matter* is invariably a constituent of the blood and may occur in the form of droplets floating in the plasma during the time when the digestive processes are active or at other times. Pathologically the increase of fat may be so great as to give the blood a somewhat milky or opalescent character. Larger masses of fat at times occur as *fat emboli*. These are portions of various adipose tissues which have become freed by traumatism or disease. Thus in fractures in which the marrow has been shattered such emboli are often formed and may lodge in the pulmonary capillaries, causing serious disturbances or even rapid death (see also Lipæmia). *Portions of tissue* of

other kinds may similarly escape into the circulation. This is exceedingly common in cases of endocarditis when fragments of the valves may be broken off; in the case of tumors (sarcoma, carcinoma, lipoma, etc.); and in eclampsia when placental cells may enter the circulating blood and lodge in the liver or lungs. *Crystalline structures* are exceedingly uncommon. In leukæmia the so-called Charcot-Neumann crystals have frequently been found in the blood post mortem and in a few instances (Westphal, Ord and Copeman) during life. More commonly these crystals do not exist in the circulating blood, but are formed after this has been removed from the body and has been suffered to undergo change under the cover glass of preparations for the microscope or otherwise. These crystals are sufficiently described in the section on leukæmia. The occurrence of similar formations in the sputa in asthma, in the seminal fluid, and in the intestinal fluids is of interest, but no explanation of their nature or significance can as yet be offered.

Micro-organisms are transported by the blood in a variety of diseases, while other forms flourish and multiply in the circulation. Among the latter the malarial parasites or *plasmodia* are of the first importance. These are animal organisms of the group of protozoa and probably complete but a part of their life cycle in the human blood. The red corpuscle is the primary seat of their growth and development. Other protozoa, notably *monadines*, have been described by Klebs, Frankenhäuser, and others in leukæmia, pernicious anæmia, and other diseases, but these observations have not been confirmed. Doubtless in many of these cases Hayem's pseudobacilli (small or fragmental red corpuscles) have been mistaken for micro-organisms. Among the higher animal forms the *Filaria sanguinis hominis* and the *Distoma hæmatobium* are important. The former does not occur in the blood in its adult form, being found then in the lymphatic channels; but the embryos are abundant in the blood of certain cases of parasitic elephantiasis, and hæmatochyluria. These embryos are small thread-like organisms about 0.0075 mm. in breadth (about the diameter of a red corpuscle) and 0.34 mm. in length. They are ensheathed by a delicate transparent capsule which is seen at each end as a closed sac. In most cases the embryos are found in the blood only at night (Filaria nocturna); occasionally they occur during the day (F. diurna) or constantly (F. perstans).

The *Distoma hæmatobium*, Bilharz, is found in the main trunk and branches of the portal vein, in the splenic and mesenteric veins, and in the veins of the bladder and rectum. Its eggs, small bodies 0.04 mm. wide and 0.12 mm. long, and carrying a sharp spicule at one

end or at the side, have been found in the lungs, liver, bladder, rectum, urethra, and urine; neither the parasite nor the eggs have thus far been met with in the blood.

Vegetable parasites or *bacteria* are frequently found in the blood. In cases of relapsing fever the spirochæta occurs so regularly that the microscopic examination of the blood is important for diagnosis. The same is true of anthrax in which the bacilli may be exceedingly abundant in the blood drawn from the skin. Among the other microorganisms that have been found in the bacteriological or clinical examinations of the blood are the pyogenic micrococci, the gonococcus, the tubercle bacillus, and the bacillus of influenza. In these cases, however, little diagnostic or clinical significance as a rule attaches to the examination of the blood for bacteria.

Clinical Methods of Examining the Blood.

Removal of the Blood for Examination.

The method of removal of the blood for various clinical examinations depends upon the purpose in view. In the ordinary examination to determine the number of corpuscles or the percentage of hæmoglobin a small incision into the end of the finger or into the lobe of the ear is painless and entirely satisfactory. The skin should always be prepared with the greatest care by carefully washing with water, drying, and then washing with alcohol. Prolonged washing or rubbing should, however, be avoided. The puncture should be made quickly, and for this purpose a flat knife, such as that used by ophthalmologists for incisions into the cornea, is very useful. Small lancets, such as those supplied with the Gowers hæmoglobinometer, in which a cap may be screwed back and forth so as to uncover any desired length of the blade, have many advantages.

In young children it may be necessary to take the blood from the great toe instead of from the finger or ear. In adults the lobe of the ear is less painful, but the flow of the blood and the manipulations can be better carried out when the end of the finger is used. Under no circumstances should peripheral congestion be induced by squeezing the finger or the like.

Larger quantities of blood are needed for certain chemical examinations, for estimations of the specific gravity, etc. Very frequently it is possible to obtain sufficient quantities for such purposes by a deep puncture into the finger, but it is much more satisfactory on the whole to introduce a fine hollow needle into one of the veins of the arm. It is exceedingly easy to insert a needle into the median basilic,

the operation is almost painless and the blood flows quickly. A light compression pad may be applied for a short time after the operation, but this as a rule is unnecessary. Repeated use of this method has convinced me that it is without danger and always easily accomplished.

Time of the Examination.—In certain examinations the time of day is of considerable importance, and it should always be stated in the records at what time the examination was made. As a rule the hours before midday are most suitable. In cases in which the number of white corpuscles or the chemical composition of the blood is under consideration, the time of the last preceding meal and the nature of the food taken should be recorded, together with the quantity of liquid consumed and the character and amount of the excretions.

Methods of Estimating the Number of Corpuscles.

Vierordt first devised a satisfactory method of counting the corpuscles of the blood. Since the time of his publication a number of methods more exact in their results have been suggested and blood-counting has come into general practice. All of the methods depend upon the determination under the microscope of the number of corpuscles in definite quantities of blood diluted with solutions which preserve the corpuscles from disintegration.

Very many solutions have been suggested for the purpose, and individual taste largely determines the preference given to one or another by various authorities. Among the more useful are the following:

Hayem's Solution.

℞ Hydrarg. bichloridi,	0.25
Sodii chloridi,	0.5
Sodii sulphatis,	2.5
Aquæ dest.,	100.0

Pacini's Fluid.

℞ Hydrarg. bichlor.,	2.0
Sodii chloridi,	4.0
Glycerini,	26.0
Aquæ dest.,	226.0

Dilute with three times the quantity of water before using.

In addition to these, simple hypertonic solutions of sodium chloride are useful and have the advantage that they are easily prepared. A one-per-cent. or two-per-cent. aqueous solution of ordinary salt answers the purpose very well. Daland and Sadler recommend a two and a half-per-cent. solution of bichromate of potassium, and I

have found this very satisfactory; but it has several times happened to me that solutions prepared with bichromate of potassium not wholly pure have been useless as they caused agglutination of the corpuscles in clusters.

The counting of white corpuscles is often facilitated by the addition of some stain such as gentian or methyl violet. This colors the white corpuscles blue and renders them more conspicuous. Toisson's fluid is exceedingly useful for this purpose. The formula is:

℞ Aquæ dest.,	160 c.c.
Glycerini,	30 c.c.
Sodii sulphatis,	8 gm.
Sodii chloridi,	1 gm.
Methyl violet,	0.025 gm.

As a rule, however, I use less methyl violet, as the red corpuscles are occasionally stained when the original formula is followed.

Sometimes it is useful to dissolve the red corpuscles so that the leucocytes may be more readily determined. For this purpose 0.3 or 0.5-per-cent. solutions of acetic acid were recommended by Thoma and have since been generally used.

A number of solutions have been suggested for counting the blood plaques. Pruss advises a mixture of ten parts of a 0.1-per-cent. chromic-acid solution with ten parts of a one-per-cent. osmic-acid solution and one part of glacial acetic acid. Afanassiew used a 0.6-per-cent. sodium-chloride solution to which 0.6 per cent. of peptone and a small amount of methyl violet had been added.

Thoma-Zeiss Method.—Among the instruments used for counting the blood corpuscles the most useful is that of Thoma, constructed by Zeiss. This consists of a pipette (Fig. 28) in which definite dilutions may be obtained and a slide upon which a layer of the diluted blood of accurate thickness is prepared. The slide is then placed under a microscope and the number of corpuscles counted within squares engraved upon the slide. In this way the number of corpuscles in definite quantities of the diluted blood can be readily determined.

The diluting pipette consists of a capillary tube about 10 cm. in length opening into a bulb at the upper end. Above the bulb the pipette again contracts to a capillary tube. The capillary tube below the bulb is graduated with cross lines marking tenths, from 0.1 to 0.5 and 1.0; above the bulb the mark 101 is found. The dilution is accomplished by drawing blood to the mark 0.5 or 1.0 and then diluting fluid until the mark 101 is reached. There is then 0.5 or 1.0 part of blood in the one hundred parts of fluid contained in the bulb. Accurate mixture is then obtained by shaking the bulb, a

small glass bead being contained in the latter to facilitate the mixing. Care must be taken in using this instrument that it is thoroughly clean and dry, and when the blood is drawn up in the capillary tube it must come accurately to the mark intended and not overshoot this mark. In the latter case it should be drawn up to the next higher mark rather than blown out, as the latter procedure would leave many corpuscles clinging to the sides of the tube. After the dilution is obtained a drop is placed upon the counting chamber (Fig. 29), care being always taken to first expel several drops of liquid from the capillary tube, as the last liquid drawn into this is liquid with which no blood has been mixed.

Fig. 28.—Capillary Tube Employed in the Thoma-Zeiss Method for Counting the Blood Corpuscles.

The counting chamber consists of a circular disc of glass cemented in the centre of a glass slide and marked by cross lines as is represented in the diagram (Fig. 30). These lines are accurately one-twentieth of a millimetre apart so that the squares formed by the intersecting lines are one-four hundredth of a square millimetre. Larger squares containing sixteen of the small ones are formed by double lines, made by drawing an extra line between two of the adjacent lines first mentioned. The disc of glass upon which these lines are drawn is surrounded by a square of glass with a circular part removed from its centre so as to enclose the first-mentioned disc. The outer table of glass is accurately 0.1 mm. higher than the inner disc, and is separated from the latter by an intervening space. A drop of the diluted blood being now brought upon the central disc of glass a ground cover-glass is applied, so that the space between the central disc and the under side of the cover-glass is accurately filled and the apposition between the outer table of glass and the cover-glass is so perfect that the Newtonian color rings are perceptible. Some practice is necessary to secure uniform results. The slide is now allowed to lie flat for some minutes so that the corpuscles may rest upon the glass disc. Then the slide is placed under a microscope (using a moderately low power, Zeiss C or Leitz 5 or 6), the Abbé condenser being removed or lowered. The cross lines are now plainly visible and the corpuscles are easily counted. In the latter process all of the corpuscles in the ruled part of the slide (containing four hundred small squares, see Fig. 30) should be counted. This insures very accurate results;

but approximate results are obtained after some experience when three or four of the large squares (containing forty-eight or sixty-

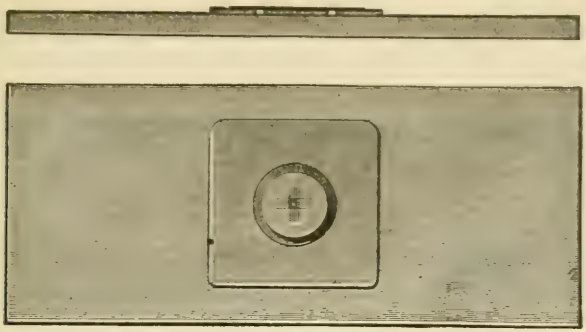

FIG. 29.—Counting Chamber Employed in the Thoma-Zeiss Method for Counting the Blood Corpuscles.

four small squares) are counted. Some rule must be adopted for the corpuscles touching the lines so as to prevent double counting or the inclusion of too large a space. If the corpuscles touching the upper line and one side line of each square (either on the inside or

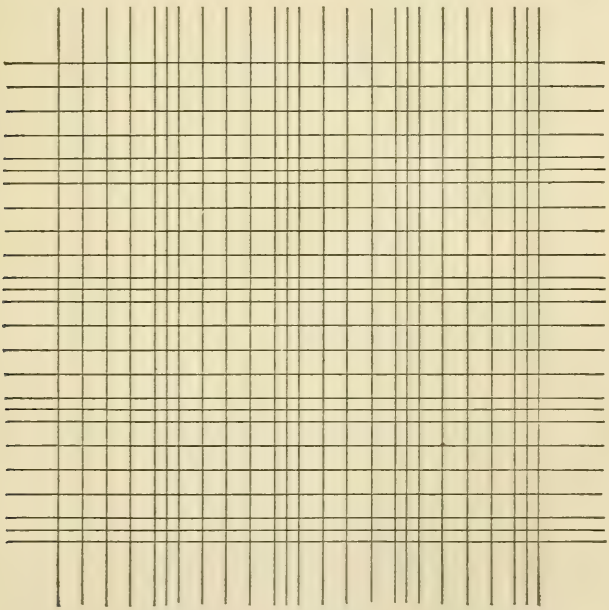

FIG. 30.—Arrangement of Cross-lines over the Counting Chamber.

the outside of the square) are included, and those touching the lower and other side line are excluded, these difficulties will be obviated.

After the corpuscles in a large number of small squares have been counted, the calculation of the number in a cubic millimetre of the blood is easily made. Each of the small squares is $\frac{1}{20} \times \frac{1}{20}$ mm. or $\frac{1}{400}$ sq.mm., and the cell is $\frac{1}{10}$ mm. deep; therefore each small square equals $\frac{1}{4000}$ c. mm. The average number of corpuscles multiplied by 4,000 therefore gives the number of corpuscles in 1 c.mm. of the diluted blood; and if this number be further multiplied by 100 or 200 (according to the dilution used) the number of corpuscles in the undiluted blood is obtained. If, for example, the number of corpuscles in 48 squares was 480, the average number is 10 per square and the calculation is: $10 \times 4{,}000 \times 100 = 4{,}000{,}000$.

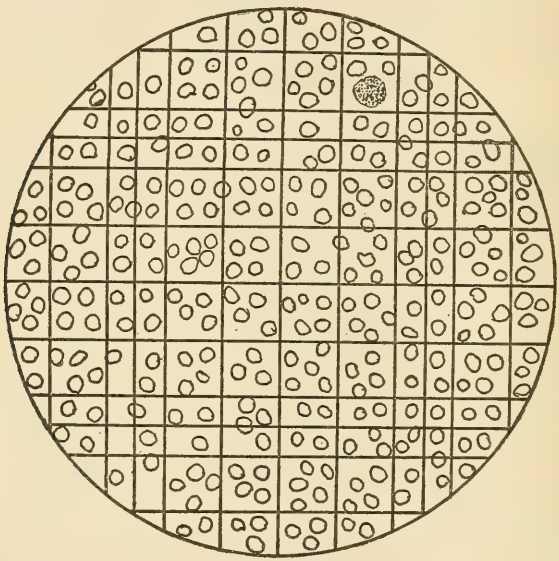

FIG. 31.—Thoma-Zeiss Method of Counting Red Blood Corpuscles. Showing the corpuscles and cross-lines under microscope. One leucocyte in the field.

The calculation is exceedingly simple when the corpuscles of the 400 squares are counted. The cubic space covering these 400 squares being 0.1 c.mm., the number of corpuscles is simply multiplied by 10 and then by 100 or 200, according to the dilution.

The white corpuscles may be estimated with the same instrument as the red, but a special diluting pipette has been prepared by Zeiss in which the dilutions 1:20 or 1:10 are obtained. When the greater dilutions (1:100 or 200) are used at least three or four slides should be prepared and the corpuscles counted in the entire ruled portion (representing 1,200 or 1,600 small squares); but even then the error is likely to be great, excepting in cases of leukæmia or decided

leucocytosis in which the number of leucocytes is very large. The method of calculation is the same as that given above.

When the special leucocyte pipette is used, it is well to select the form in which the capillary tube is greatly contracted at the tip. This makes it easy to draw the blood up slowly and accurately to the mark intended. The acetic acid mixture is always desirable as a diluent to be used with this pipette, as the number of red corpuscles in a 1:10 or 20 dilution is so great that they may interfere with the counting of the leucocytes.

The estimation of the number of leucocytes may be greatly facilitated by determining the area covered by the field of vision of the microscope and then counting the leucocytes in a large number of such fields. The area of the field is readily determined by moving the tube of the microscope up or down until one of the parallel lines

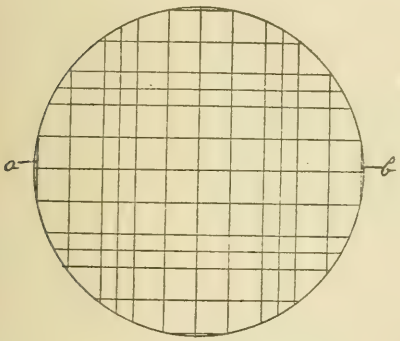

Fig. 32.

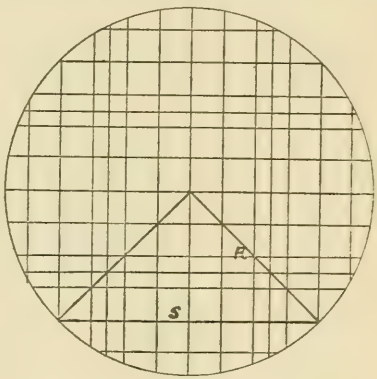

Fig. 33.

of the ruled slide accurately coincides with either side of the field of vision, as in Fig. 32. The diameter of the field is then $\frac{a}{20}$ mm. (a being the number of parallel spaces included in the field). The area of the circle is readily calculated by the formula $R^2\pi$ (R = radius; π = 3.1416), or substituting the figure representing R, it is $(\frac{a}{40})^2\pi$. The cubic content of the space under the field of vision is $\frac{1}{10}\times(\frac{a}{40})^2\pi$ (*i.e.*, depth of the chamber multiplied by the surface area). If, for example, 8 parallel spaces are included, the formula would be: $\frac{1}{10}\times(\frac{8}{40})^2\pi$ or $\frac{1}{10}\times\frac{1}{25}\times 3.1416$. If in this case the corpuscles in 25 full fields of vision were counted and the dilution was 1:10, the total number of corpuscles in the 25 fields would simply be multiplied by 3.1416 to obtain the number of leucocytes in 1 c.mm. of undiluted blood. If the number of leucocytes is greatly above the normal, it would, however, prove difficult to count the corpuscles in so large a field without the aid of cross lines. In such cases a dilution of 1:100 should be

used and the calculation altered accordingly. The same method of calculation may be applied to any number of parallel spaces; and if the tube is marked and the same lenses are always employed, the factor will remain constant for all subsequent calculations.

The same result is accomplished by moving the tube of the microscope until the corners of a square group of smaller squares are cut by the field of vision as in Fig. 33. The area of the field of vision may then be readily determined by its relations with the area of the enclosed square. Thus in Fig. 33 a square is enclosed, each side of which is eight spaces in length. Representing this by S, the area of the square $= S^2$. The radius (R) of the circle may be de-

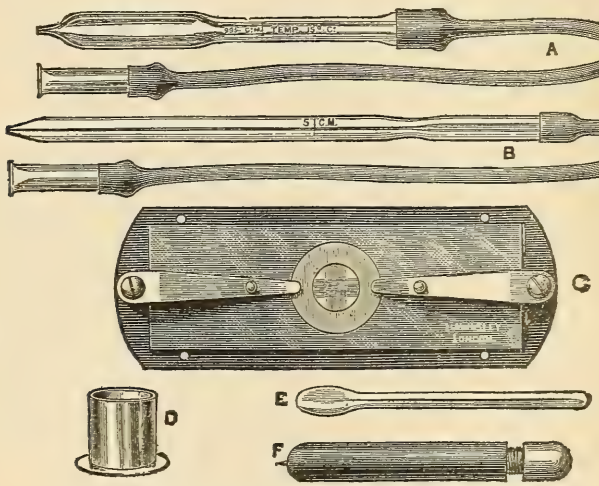

Fig. 34.—Gowers' Hæmacytometer.

termined from the relations of the right angle. Thus $S^2 = 2R^2$, or $R^2 = \frac{S^2}{2}$. The area of the circle being $R^2\pi$, the terms may be changed so that the formula is obtained:

$$\text{Area of circle} = \frac{S^2}{2}\pi$$

and

$$\text{area of square} : \text{area of circle} :: S^2 : \frac{S^2}{2}\pi;$$

or

$$\text{area of square} : \text{area of circle} :: 2 : \pi.$$

From this formula the calculation is easily accomplished in any case, no matter how many squares are included in the circle or what is the degree of the dilution.

Gowers' Hæmacytometer.—This instrument consists of a pipette, in

which exactly 995 c.mm. of liquid may be measured, and of a capillary tube graduated to contain 5 c.mm. A small glass jar is furnished for mixing the blood and diluting fluid, and a glass rod is used for stirring the mixture. A brass stage plate carries a glass slip, on the centre of which is a cell $\frac{1}{5}$ mm. deep and divided into squares $\frac{1}{10}$ mm. on each side by parallel lines crossing at right angles. A cover-glass is pressed upon the cell by brass clips attached to the stage plate. This instrument is used as follows: 995 c.mm. of a diluting fluid are placed in the mixing jar and 5 c.mm. of blood are measured in the capillary tube and then added to the diluting fluid. Thorough mixture of the fluids is secured by stirring with the glass rod; a drop of the diluted blood is then placed upon the cell and covered with a ground cover-glass held in place with the clips. After a few minutes the number of corpuscles in the cell is counted and the result is easily calculated. Each square represents a cubic space of $\frac{1}{5000}$ c.mm. ($\frac{1}{5}\times\frac{1}{10}\times\frac{1}{10}$) and the dilution is 1:200. Therefore the number of corpuscles in 10 squares multiplied by 10,000 gives the total number in 1 c.mm. of undiluted blood. This instrument is upon the whole less useful and more complicated than the Thoma-Zeiss apparatus.

Other instruments have been constructed by Mallassez, Alferow, and others, but those described, particularly the Thoma-Zeiss, answer well for all practical purposes.

Determination of the Volume of the Corpuscles.

A number of methods have been suggested for this purpose. In practical clinical work the centrifugal apparatus of Blix-Hedin is the readiest and most reliable method, though the results are less accurate than those obtained by certain more tedious and complicated methods, such as that of the brothers Bleibtreu.

Blix-Hedin Hæmatokrit.—The method of applying centrifugal force in the separation of the corpuscles from the plasma or serum was employed by Gamgee and Blix, and the latter constructed a special instrument, the hæmatokrit. This was subsequently improved by Hedin and has since been modified in some particulars by Daland and Gaertner. It consists of a metallic frame in which two capillary tubes may be revolved in a horizontal direction with great speed (9,000 to 10,000 revolutions per minute). The tubes are 35 mm. long and have a uniform diameter of 1 mm. They are divided into fifty parts by cross rulings. In the practical use of this instrument the blood is first diluted with an equal quantity of Müller's fluid, or two and a half per-cent. solution of bichromate of potassium, the Thoma-Zeiss pipette for white corpuscles or special capillary tubes (Hedin) being used for this purpose. The mixture is placed in a small dish, and the capillary

tubes are filled by placing one end in the liquid and sucking through a rubber tube applied to the other end. The tube is then placed in the metallic frame, where it is held in place by springs, the ends being firmly closed by caoutchouc caps. Both tubes being in place, the sedimentation is accomplished by rapid revolutions continued for a minute or more. Usually one minute suffices to secure a constant volume of red corpuscles in the distal end of the tubes, where a dark, colored mass will be observed. At the inner end of this mass the leucocytes collect in a light gray or whitish zone and the proximal

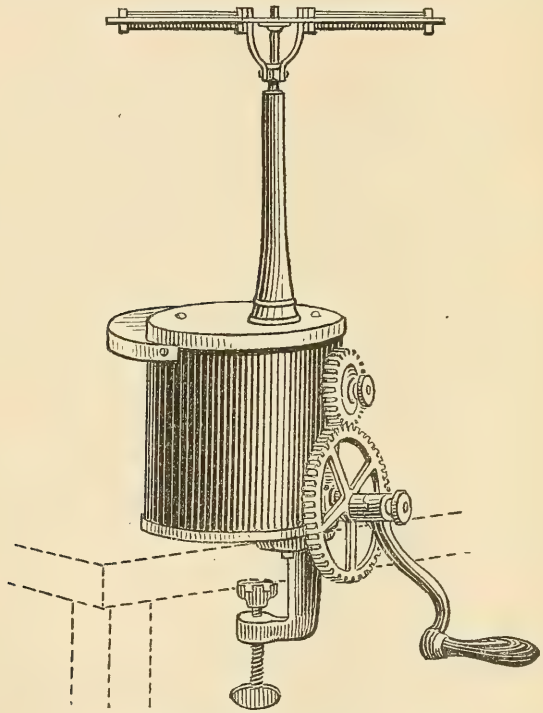

Fig. 35.—Hæmatokrit. Daland's modification.

part of the tube is occupied by the yellowish mixture of plasma and diluting fluid. The volume of red corpuscles is then read by placing a piece of white paper beneath the tube and counting the number of spaces filled by the corpuscles. This number multiplied by 4 gives the volume of red corpuscles in 100 parts of blood, since the blood has been diluted with an equal bulk of diluting fluid, and the tube is divided into 50 parts. In Daland's investigations the volume of blood corpuscles in normal subjects varied from 44 to 66 parts in 100, the average in 55 cases being 51.618. The white corpuscles cannot be accurately determined, though in cases of leucocytosis a

considerable increase of the usual volume may be observed. The volume percentages may be used to calculate the approximate number of corpuscles. Thus in Daland's studies the average number of corpuscles counted by the Thoma-Zeiss apparatus was 5,130,248 and the average volume 51.618. One volume, therefore, corresponded to about 99,390 red corpuscles. Alterations in the size of the corpuscles make a great difference in the total volume, so that a conversion of volume into number percentages might be quite unreliable.

The centrifugal apparatus is extremely useful in scientific studies, but cannot in its present form supplant the Thoma-Zeiss counting method in ordinary clinical work. The method is much simplified by substituting longer tubes divided into hundredth-volumes instead fiftieths and by working rapidly with undiluted blood. Absolutely accurate results cannot, however, be obtained.

Sedimentation Methods.—Methods of this kind have been employed by a number of investigators, and particularly by Biernacki. The blood is defibrinated or treated with oxalate of sodium to prevent coagulation, and placed in a tall and accurately graduated cylinder. After twenty-four or forty-eight hours a sediment of corpuscles of constant height is obtained and the volume is readily calculated. This method, however, can give only approximate results.

The Bleibtreu method, introduced by the brothers Bleibtreu, is the most scientific of those thus far suggested. Two or more parts of blood are diluted with known quantities of 0.6 per cent. NaCl solution and the corpuscles allowed to settle. The clear serum is then removed with the aid of a pipette and the amount of nitrogen in this is determined by the Kjeldahl method. The volume of the serum may be readily determined by comparison of the amounts of nitrogen in equal quantities of the different specimens of diluted plasma, or of that in the diluted plasma and that in the undiluted plasma obtained by sedimentation of the blood. The following formula serves for the calculation:

$$x\,(n_1 - n_2) = n_2 \frac{s_1}{b_1} - n_1 \frac{s_1}{b_1},$$

n_1 and n_2 being the amounts of nitrogen in equal parts of two specimens of serum differently diluted; s_1 and s_2 being the quantities of sodium chloride solution employed, and b_1 and b_2 the quantities of blood.

Undoubtedly objections may be made against this method, and in particular it is certain that the sodium-choride solution causes some change in the red corpuscles by osmosis; but upon the whole the method is the most reliable yet devised. Greater accuracy is obtained by first determining the isotonicity of the red corpuscles and using the

isotonic strength of NaCl; but this makes the examination more tedious.

Differential Counting of the Leucocytes.

The counting of the individual forms of leucocytes in the stained specimen of blood is a rather tedious process. Ordinarily this is done by preparing a cover-glass or a number of cover-glass preparations, staining with the triacid mixture, and moving the specimen about with the aid of a mechanical stage. In this way a large number of leucocytes may be counted and the relative proportions established. Not less than five hundred or one thousand white cells should be estimated.

Zappert recommended the following method: To a freshly prepared osmic-acid solution he adds a few drops of a filtered mixture composed of equal parts of distilled water and glycerin, and half as much of a one-per-cent. solution of eosin in water. The solution thus prepared is used as a diluting mixture with the Thoma-Zeiss apparatus. The eosinophilic cells according to Zappert are readily determined, but my own experiences with this mixture have been very unsatisfactory.

Elzholz has suggested a mixture which seems to be more satisfactory. Using the Thoma-Zeiss mélangeur for white corpuscles, blood is drawn to the mark 1, and then the following mixture until the bulb is half filled: Aqueous solution of eosin (two per cent.), 7 parts; glycerin, 45 parts; and distilled water, 55 parts. The blood and liquid are shaken for a few minutes, and then a second solution (composed of concentrated aqueous solution of gentian violet, 4 drops; absolute alcohol, 1 drop; and water, 15 c.c.) is drawn into the pipette until the mark 11 is reached. The polymorphous cells are deeply stained, the eosinophilic reddish-violet.

Estimation of the Amount of Hæmoglobin.

A number of methods have been suggested for this purpose. They depend, for the most part, upon comparisons of diluted blood with colored solutions of various kinds, or with other standards, or upon the thickness of layers of blood through which marks or other objects may be plainly visible. The best known and most satisfactory methods are those of Fleischl, Gowers, and Hoppe-Seyler.

Fleischl's Method.—The apparatus consists of several parts. There is first a metallic cylinder with a glass bottom and divided into two equal parts by a vertical septum. The blood is placed in one-half of the cylinder, water in the other half. Measuring pipettes are supplied so that the exact quantity of blood for each individual instrument may be obtained. A wedge of red glass mounted in a frame

which moves horizontally beneath a stage furnishes the standard with which the diluted blood is compared.

In the practical application of this instrument one of the pipettes is filled with blood by capillarity. The blood is placed in one compartment of the metal cylinder, and the compartment then filled to the top with distilled water; the other side of the cylinder is filled with water. The cylinder is placed over a circular opening in the stage, where it rests directly above the wedge of glass, which may be moved back and forth on the under side of the stage. Light from a candle

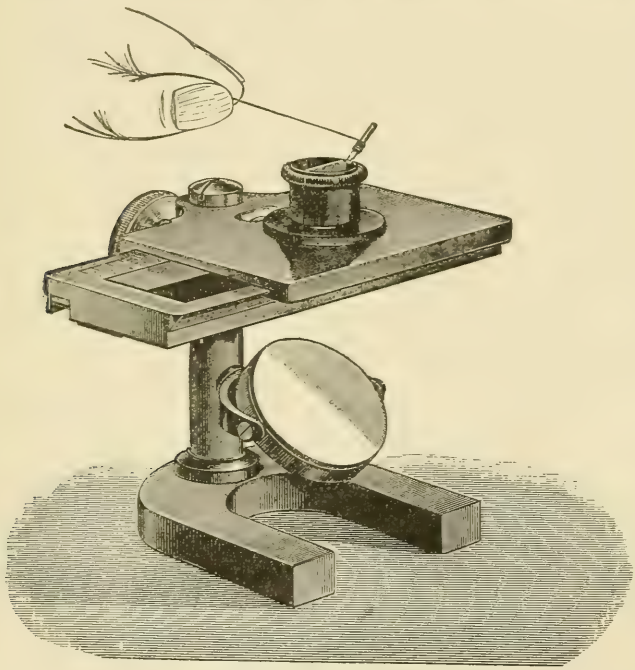

Fig. 36.—Fleischl's Hæmoglobinometer.

or lamp (daylight cannot be used) is reflected upwards from a plaster-of-Paris plate, and as the wedge of glass is moved its color, seen through the distilled water in the one side of the cylinder, is compared with that of the diluted blood in the other side. A scale is engraved upon the frame carrying the wedge of glass in such manner that with normal blood the two colors are alike when the frame stands at the mark 100. From this mark towards the thin, light-colored end of the glass wedge the numbers 90, 80, 70, etc., are found, and thus the percentage proportion of hæmoglobin is readily determined by moving the glass wedge back and forth. The absolute amount of hæmoglobin is easily calculated when it is remembered that there are about

14 parts of hæmoglobin in 100 parts of normal blood. The number 14 is simply multiplied by the percentage number and divided by 100. Thus if 80 per cent. of hæmoglobin is found, the absolute quantity of hæmoglobin is $80 \times 14 \div 100 = 11.20$.

There are several inaccuracies in this method. In the first place, the normal number 100 is too high, many individuals having apparently normal blood showing only 85 or 90 per cent. by the Fleischl method. In the second place, the comparison of colors is difficult when the blood is poor in coloring matter, and the error grows with decreased amounts of hæmoglobin so that the determination of very small quantities is quite inaccurate. This error may be obviated in part by taking blood from two pipettes instead of from one and dividing the percentage by two. On the whole, Fleischl's instrument is the most useful one devised for ordinary clinical work.

Gowers' Hæmoglobinometer.—The instrument consists of two glass cylinders, one containing a standard carmine-picrocarmine-glycerin solution corresponding to a one-per-cent. aqueous solution of normal blood; the other is graduated in tenths from 10 to 120. A capillary tube marked so that exactly 20 c.mm. may be measured is used to secure the proper quantity of blood, and a small dropper is supplied to add distilled water to the blood.

The estimation is conducted as follows: A drop or two of distilled water is placed in the graduated glass cylinder. Then 20 c.mm. of blood are measured in the pipette and carefully expelled into the cylinder. The cylinder is shaken for a few minutes and then distilled water is added with the dropper until the blood is diluted to a point at which the color is exactly that of the standard. This is readily determined by holding the two cylinders against a sheet of white paper. The proportion of hæmoglobin is then obtained by noting on the scale the figure to which the dilution has been carried.

Hoppe-Seyler's apparatus is too complex to be described in this place. It consists of a metal tube and prismatic mechanism by which the color of a standard solution of CO-hæmoglobin may be compared with that of a quantity of blood treated with carbonic oxide and diluted with water saturated with the same gas. The results obtained by this method are more accurate than those obtained by the Fleischl or Gowers apparatus, but the method is too difficult for ordinary clinical work.

The instruments of Hayem, Henocque, Bizzozero, and Mallassez are inferior and little used. Henocque's method is described in the following section.

Spectroscopic Examination of the Blood.

The spectroscope is useful to determine the form of the hæmoglobin present in the blood. Under normal conditions this substance, which constitutes nearly 14 parts in 100 parts of the entire blood, occurs as an oxy-compound, called oxyhæmoglobin. The latter is an albuminous iron-containing body, four per cent. being hæmochromagen and 96 per cent. albumin. The hæmoglobin is retained in the body of the corpuscle by the stroma of the latter, but is rather easily dislodged and the oxyhæmoglobin may thus become dissolved in the plasma (hæmoglobinæmia), and rhombic plates or crystals of oxyhæmoglobin may appear within the living body. The oxyhæmoglobin is a loose compound of one molecule of oxygen with one of hæmoglobin, and readily parts with its oxygen in vacuo or under the influence of various reducing agents.

Spectroscopically, *oxyhæmoglobin* is distinguished by a darkening of each end of the spectrum, notably at the indigo end, and by two rather broad absorbent bands in the yellow and green between the lines D and E. When submitted to the action of reducing agents oxyhæmoglobin is converted into *reduced hæmoglobin* or simple *hæmoglobin*. The appearance of the blood to the naked eye undergoes a change when this reduction takes place, the color becoming a dark bluish-red instead of the normal light red, and the spectroscope shows a single absorption band instead of a double band between D and E. Acids and alkalies further reduce or break up the hæmoglobin, producing an albuminous body, and an iron-containing pigment known as *hæmatin*. Under the influence of salt solution and acetic acid the oxyhæmoglobin may be converted into a chlorine compound of hæmatin, called *hæmin*. The latter crystallizes in elongated rhombic plates of brown color. Its spectroscopic features are the same as those of hæmatin. By treating either of these compounds with strong sulphuric or hydrochloric acid, the iron may be abstracted and a pigment results which is isomeric with bilirubin and known as hæmatoporphyrin. The spectrum of hæmatin in alkaline solution shows an absorbent band lying between C and D, and slightly beyond D. In acid solution the lines are identical with those of *methæmoglobin* in acid solution. The last-named form of hæmoglobin is produced by a large number of blood poisons. It is an oxygen compound of the hæmoglobin in which the oxygen is in more intimate union with the hæmoglobin than in oxyhæmoglobin, though the relative quantities are the same. The close association reduces the value of the hæmoglobin in this form for purposes of oxygenation. The spectrum of this compound is the same as that of

hæmatin in acid solution. In acid or neutral solution it is distinguished by four absorbent bands, the most distinct being between C and D, two others between D and E, each of them lying in immediate relation with the lines, and the fourth between *b* and F, near to F. Methæmoglobin may be distinguished from hæmatin by the careful addition of sulphide of ammonium, which causes a conversion into oxyhæmoglobin and then to reduced hæmoglobin, while the hæmatin in acid solution after treatment with sulphide of ammonium shows the spectrum of reduced hæmatin marked by two lines between D and E, the latter of the two crossing E almost as far as *b*.

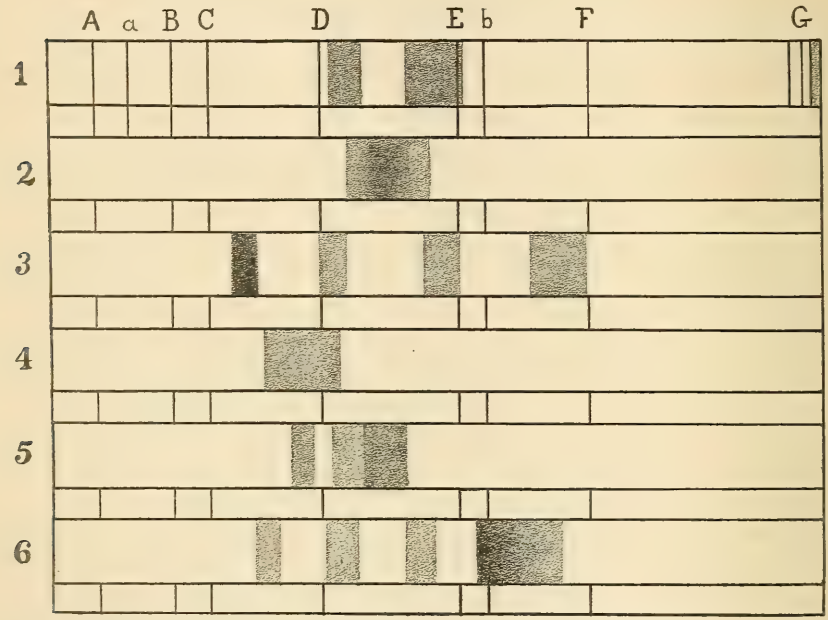

FIG. 37.—Spectra of the Blood (after Neumeister). 1, Oxyhæmoglobin; 2, reduced hæmoglobin; 3, methæmoglobin in acid or neutral solution; 4, hæmatin in alkaline solution; 5, hæmatoporphyrin in acid solution; 6, hæmatoporphyrin in alkaline solution.

Hæmatoporphyrin shows a small absorption band between C and D, near to D, and especially a dark band between D and E, near to D. In alkaline solution four bands are seen: one between C and D, near D; two between D and E, each near these lines; and a fourth, broad and very dark, between *b* and F.

Certain other combinations, such as CO-hæmoglobin, may be recognized by the spectral bands. CO-hæmoglobin is distinguished by two bands resembling those of oxyhæmoglobin, though they are displaced somewhat farther to the right, and the addition of sulphide of ammonium does not effect a reduction to reduced hæmoglobin as is the case

with oxyhæmoglobin. The combinations with cyanogen and sulphuretted hydrogen are unimportant.

In the spectroscopic examination of the blood or of liquids containing blood the small spectroscope of Browning may be employed with advantage, but for careful examinations larger instruments are needed. Daylight or lamplight may be used, and after the spectrum has been adjusted a small amount of the liquid for examination is placed in a glass vessel having parallel walls and held between the light and the linear aperture in the front of the spectroscope.

When blood is to be examined it should be diluted with distilled water and examined at once. When serum or plasma is to be examined the blood should be drawn with the greatest care and placed upon ice or in the refrigerator until the corpuscles have precipitated. The plasma is then carefully pipetted and examined as such or first diluted. The various reducing agents may be applied to distinguish forms having similar appearances in the spectroscopic examination.

Henocque has very ingeniously applied the method of spectroscopy in clinical examinations. Using his instrument in which a layer of blood of gradually increasing thickness is prepared, he examines with a spectroscope to determine at what point the oxyhæmoglobin bands are plainly visible. The thicker the layer of blood the less hæmoglobin is indicated, and the percentage proportion is readily calculated. This method, however, has no advantages over the simpler methods of Fleischl and Gowers.

Henocque has further devised a method for estimating the rapidity of the reduction of oxyhæmoglobin to reduced hæmoglobin in the living body. The spectroscope is applied to a transparent part, such as the lobe of the ear or the end of a finger, and the circulation stopped by pressure or by a ligature. The rapidity with which the spectrum of oxyhæmoglobin disappears and that of reduced hæmoglobin is developed may be readily determined. In health it usually requires about seventy seconds; in severe anæmia thirty seconds may suffice.

Methods of Determining the Specific Gravity of the Blood.

Method of Hammerschlag.—A series of mixtures of chloroform and benzol is prepared in such manner that the specific gravity increases from about 1.035 to 1.060. A drop of blood is brought into each mixture, and the one noted in which the drop neither sinks nor rises. This mixture has the same specific gravity as the blood. The operation is facilitated by using a fine capillary tube bent at a right angle at one end. The drop of blood is expelled from this in the middle part of the mixture contained in a tall vessel.

The methods of Roy and Fano depend upon the same principle, but other mixtures are employed. All of these methods are liable to errors, but for clinical purposes are perhaps sufficiently accurate and to be recommended on account of their simplicity.

Method of Schmalz.—This is by far the most accurate method, though it requires accurate chemical balances. A small capillary tube or cylinder (pyknometer) of known weight, having thin walls, is filled with blood and carefully weighed. The weight of blood is obtained by subtraction, while that of the same amount of water being known from previous estimation, the specific gravity is obtained by dividing the weight of blood by the weight of water. The same method is applicable in the estimation of the gravity of the serum or plasma.

A very convenient form of pyknometer is one made of cylindrical shape and closed by a glass stopper through the long axis of which a capillary tube is hollowed out. The pyknometer is filled with blood, the stopper pressed in firmly, and the excess of blood which has escaped through the capillary tube or around the sides of the stopper carefully wiped away.

Determination of the Rapidity of Coagulation.

A. E. Wright has devised a simple and useful method. A leather vessel surrounded by small pouches is prepared so that warm water may be used in the reservoir to keep the blood placed in the pouches at an even temperature of 18.5° or 37° C. The blood is drawn into small glass capillary tubes so that a column about 5 cm. long is formed. This is drawn up so that the end of the capillary tube is free. Several such tubes being prepared and placed in the pouches of the reservoir, tests may be made at regular intervals of a half or one minute to determine the time at which the blood cannot be blown from the tube. The time of preparation having been noted for each tube, the rapidity of coagulation is readily determined from the time at which the first coagulation is observed.

Methods of Determining the Alkalinity of the Blood.

The *alkalimetric methods* have as their object the determination of the alkaline constituent of the blood. The objections to these methods have been referred to in the consideration of the chemistry of the blood.

Landois' Method.—This method consists in the neutralization of the blood with solutions of tartaric acid. Ten solutions of weak tartaric acid and neutral sulphate of sodium are prepared in such manner that the quantity of acetic acid increases, and that of sodium sul-

phate decreases, from one to ten. A capillary pipette is prepared so that the diluting and neutralizing fluid may be drawn to a certain mark, and then an equal quantity of blood when the whole column of liquid has reached a second mark. The mixture is then expelled into a watch glass and carefully tested with litmus paper to note the mixture with which the first evidence of acidity is noted. A table constructed for this test gives the percentage of NaHO corresponding to each mixture.

Schultz-Shultzenstein's method is useful clinically, principally on account of the small amounts of blood required. A small tube containing a definite quantity of blood (7.5 mgm.) is filled by capillarity, then diluted to 12 c.c. with absolutely neutral water; 1.5 c.c. of a $\frac{1}{100}$ normal sulphuric-acid solution is then added, an ethereal solution of erythrosin being used as an indicator. The mixture is titrated with $\frac{1}{600}$ normal potassium hydrate solution and the point is noted when the indicator shows the first change to red. The amount of alkalinity is readily determined by the amount of potassium hydrate solution required less than that which would be necessary for the unaltered acid first used.

v. Limbeck's method is the most scientific, but too cumbersome for ordinary clinical work. It may be applied to the blood as a whole or to the serum. About 200 c.c. of distilled water are heated to the boiling point and 5 c.c. (for serum) or 10 c.c. (for total blood) of $\frac{1}{10}$ HCl added. The serum or blood is then carefully added drop by drop with a stirring rod until 5 c.c. are added. Titration with 1:10 NaHO is then practised until a heavy flocculent precipitate is formed. There is from the first slight opalescence; the precipitate appears suddenly and does not disappear on agitation. The alkalinity is readily calculated from the amount of NaHO used.

Methods of Determining the Isotonic Relations of the Corpuscles and Plasma.

Isotonicity of the Corpuscles.—Into a number of test glasses are placed 10 or 20 c.c. of solutions of NaCl varying in strength from 0.3 to 0.6 per cent., and each succeeding solution being 0.02 per cent. more concentrated than the next preceding one. About 0.5 c.c. of blood is added to each glass and the mixture of the fluids secured by gentle agitation. The glasses are placed aside and after twenty-four hours are examined to determine in which solution the first evidence of dissolution of the red corpuscles with solution of the hæmoglobin in the saline fluid makes its appearance. The solution next to this is the isotonic solution, and the isotonicity of the red corpuscles is expressed in terms of NaCl, the strength of the isotonic

solution being thus indicated. In normal conditions the isotonic strength for human red corpuscles is about 0.46 per cent.

In my own experiments with this method I have used smaller quantities of blood. I first prepare small cylindrical tubes with one end closed and rounded, by drawing out glass tubing and sealing one end. These are about 4 cm. long and 7 mm. in diameter. The blood is drawn from the punctured finger to the 0.5 mark of a Zeiss leucocytometer pipette, and the diluting fluid to the 11 mark. The mixture is quickly expelled into the small tubes. A number of mixtures are thus prepared with saline solution varying in strength from 0.4 to 0.6 per cent. Instead of setting these aside for gradual sedimentation I place them in a centrifugal apparatus after a few minutes, and the whole examination is completed in fifteen or twenty minutes.

Hypertonicity of the Plasma.—Serum, plasma, or other liquids, the hypertonicity of which is to be determined, are diluted with definite quantities of water and placed in small test glasses. The quantity should be about 10 c.c., and the dilutions should be gradually increased from the beginning to the end of the series. A drop of blood is placed in each glass and well mixed with the liquid. After twelve or twenty-four hours the solution which is exactly isotonic is determined as in the NaCl method described above, and the isotonicity of the blood corpuscles of the blood used being known or determined at the same time, the hypertonicity of the plasma is easily calculated by the formula—

$$\text{Hypertonicity} = \frac{a+b}{a} \times c,$$

a being the quantity of plasma used, b being the amount of water added, and c the isotonicity of the blood corpuscles of the blood used in the test. For example, if 5 parts of plasma and 4 of water are used and the isotonicity of the corpuscles is 0.45, the hypertonicity is—

$$\frac{5+4}{5} \times 0.45 = 0.81 \text{ per cent.}$$

Determination of the "Resistance" of Red Corpuscles.

Lakers has devised a method of studying the resistance to electrical influences, while Maragliano has determined the effect of thermic and other influences. These methods, however, are of little practical value.

Histological Examination of the Blood.

The blood may be examined in its fresh state or it may be fixed upon glass slides or cover-glasses and subsequently stained.

The Fresh Blood.—The cover-glasses and slides used in the exam-

ination should always be cleaned with the most scrupulous care. The fresh glasses may be cleansed with solutions of bichromate of potassium and sulphuric acid, and later with nitric acid and alcohol. A cover-glass properly cleaned is held with forceps and is brought into contact with the top of a drop as it appears upon the skin, the first few drops escaping from a puncture always being discarded. The cover-glass is then quickly laid upon the slide, when the blood will spread into a thin layer by the weight of the cover-glass alone. When a prolonged examination is desired or necessary, the edge of the cover-glass should be surrounded by vaseline or some other oily substance to prevent evaporation. The examination is made first with a low power and then with the oil immersion lens. The appearance of the corpuscles, their general shape and size, and the formation of rouleaux will in a general way give evidence of the condition of the blood. Some opinion may also be formed of the coagulability by the fibrin network passing between the corpuscles. Malarial organisms, filaria, and other parasites are easily detected after a little experience. When the amœboid movements of the corpuscles are to be determined the slide should be placed upon a warming stage and kept at an even temperature, but for ordinary purposes this is unnecessary.

Examination of the Fixed Blood.—These methods of blood examination are largely the result of the investigations of Ehrlich and his pupils. The examinations comprise (1) the proper spreading of the blood upon cover-glasses or glass slides; (2) fixing; (3) staining.

Preparation of the Blood.—The cover-glasses must be absolutely clean and should be held with forceps rather than with the fingers. The top of a drop of blood as it emerges from the punctured skin is touched with the cover-glass and this is quickly placed upon another cover-glass so that the blood spreads into a thin film. With the aid of a second pair of forceps the two cover-glasses are then drawn apart as in the preparation of sputum for microscopic examination. The same result may be accomplished by using glass slides with accurately ground edges. The edge of one of the slides is drawn across the top of a drop of blood and this edge is then applied to the second slide and rapidly carried over its surface, leaving a thinly spread film of blood. The cover-glass method, however, is in general more satisfactory. After the blood has been spread the glasses are allowed to dry in air and should ordinarily be left for at least an hour before further examination is attempted. For rapid clinical work, however, the blood may be at once fixed. Specimens thus prepared and dried in air may be preserved without further preparation for great lengths of time.

Fixing.—The blood must be fixed before any attempt is made to stain the specimen, as the solutions used for the latter purpose fre-

quently dissolve the hæmoglobin from the corpuscles or wash the blood from the slide.

For the finer examinations accurate fixation is necessary to demonstrate the detail of structure of the corpuscles, particularly that of the leucocytes. Among the methods advocated the most useful are fixation by heat and by mixtures of absolute alcohol and ether. Heating may be accomplished by placing the cover-glasses according to Ehrlich's method upon a brass plate heated at one end with a Bunsen flame. A brass plate about eighteen inches long, five inches wide, and an eighth of an inch in thickness is admirably adapted to this purpose. The point at which the cover-glasses should be placed is determined after the Bunsen flame has heated the plate to a more or less fixed point. Drops of water are then placed upon the plate with a pipette, and the point noted at which the water does not assume the spheroidal state but rapidly evaporates. The temperature at this point is about 110° to 130° F., and the cover-glasses properly dried in air should be arranged along this line or slightly farther from the flame and heated for a half-hour or several hours. The plate should always be placed in a hood or other place free of draughts. More accurate heating, however, may be secured by placing the cover-glasses in a hot-air oven and maintaining the temperature at about 120° C. Nikiforoff advises the use of equal parts of absolute alcohol and ether, and for ordinary clinical purposes this is the most useful method. The preparation should be allowed to remain in the mixture for fifteen or twenty minutes, but for rapid work from three to five minutes will suffice. Solutions of bichloride of mercury, of picric acid, and other reagents may be used for the demonstration of karyokinesis or for other special purposes.

The staining methods of Ehrlich depend primarily upon certain facts regarding the nature and action of the aniline dye-stuffs. These may be divided into two primary groups, the acid and the basic. The former group includes those in which the acidulous part of the compound is the active staining agent, as picric acid in picrate of ammonium; the latter, those in which the base of the compound is the staining element, as in acetate of rosanilin or fuchsin. Subdivisions of these groups have been distinguished and the individual stains differ in the *intensity* with which they stain certain cellular elements and their *affinity* for the same. A certain cellular constituent may have as great an affinity for certain stains as for others, while the intensity of the stain may vary greatly; and the reverse. Mixtures of acid and basic stains may be prepared in such manner that a neutral stain results, and cellular elements may be distinguished by their special affinity for such combinations.

Oxyphilic Mixtures.—Of the acid stains eosin ranks as the most important. A simple solution of eosin in sixty-per-cent. alcohol acts very well for ordinary purposes.

Eosin,	1.0
Alcohol, sixty per cent.,	100.0

The oxyphilic or eosinophilic granules are stained intensely red or pink with this solution. The red corpuscles are stained less intensely red.

Contrast staining of the nuclei of the white corpuscles may be obtained by staining the specimen with Delafield's hæmatoxylon after they have been treated a few minutes with the eosin mixture. The hæmatoxylon solution acts rapidly, staining intensely in a minute or less. The specimen is then washed, dried, and mounted.

A combination of eosin and hæmatoxylon has been suggested by Gollasch:

Eosin crystals,	0.5
Hæmatoxylon,	2.0
Glycerin,	
Distilled water,	
Absolute alcohol,	āā 100.0
Glacial acetic acid,	10.0
Alum,	slight excess.

The solution must be allowed to stand in a light place for several weeks. Only the oxyphilic granules are stained by the foregoing methods.

Combinations of eosin and methyl blue may be used to demonstrate the basophilic granules, and the same mixtures are also admirable for the manner in which they show the simple morphology of the leucocytes.

The specimen of blood may be first stained with the weak alcoholic eosin solution, washed in water, and then treated for a short time with a saturated solution of methyl blue diluted somewhat at the time of using. The methyl blue must not be allowed to act above a half minute or a minute, as there is a tendency to overstain. The same result is obtained by combinations like the following:

Chenzinsky's Solution.

Saturated aqueous solution of methyl blue,	40 parts.
Eosin solution, one-half per cent. in seventy-per-cent. alcohol,	20 "
Glycerin,	40 "

Klein's Solution.

Methyl blue,	3.0
Distilled water,	100.0

Dissolve and add

Alcohol,	5.0
Eosin (soluble in water),	0.5

This last solution is to be well stoppered and placed in an oven at body heat for several hours. A few drops of alcohol should be added from time to time.

CANON'S SOLUTION.

Methyl blue, saturated aqueous solution,	40 parts.
Eosin, one-half or one-quarter per cent. in seventy-per-cent. alcohol,	20 "
Distilled water,	40 "

The specimen is stained from three to six or more hours in an oven kept at a temperature of 37° C. All of these mixtures show the oxyphilic as well as the basophilic granules very distinctly.

Solutions of eosin in glycerin give more beautiful results than the aqueous solutions, though they are far less generally useful and are more troublesome. A saturated solution of eosin in glycerin, or, better, in five-per-cent. carbol-glycerin may be used, or the following preparation of Huber may be employed:

Aurantia,	
Indulin,	
Eosin,	āā 2
Glycerin,	30

Solution is effected by prolonged shaking or stirring, and the glycerin should be moderately warmed. The red corpuscles are stained orange by the aurantia, the nuclei purple by the indolin, and the oxyphilic granules red by the eosin. The best results are obtained when the blood is fixed by prolonged heating.

Basophilic Mixtures.—The methyl-blue solutions already named are useful. In addition solutions of dahlia are advantageous.

EHRLICH'S FORMULA.

Dahlia, saturated alcoholic solution,	50
Glacial acetic acid,	10 to 20
Distilled water,	100

The best results are obtained by following Müller's method. The preparation is heated for several hours, then further fixed in absolute alcohol for several days (this is not entirely necessary), stained with dahlia several hours, washed in water a long time, in alcohol a considerable length of time, dried, and mounted.

Neutrophilic Mixtures.—Ehrlich first recommended the following:

Saturated aqueous solution orange G,	125
Saturated solution acid fuchsin in twenty-per-cent. alcohol,	125

Add with constant agitation:

Saturated aqueous solution methyl green,	125
Absolute alcohol,	75

More recently Ehrlich has altered the formula as follows:

Saturated aqueous solution orange G,	120 to 135
Saturated aqueous solution acid fuchsin,	80 to 165
Saturated aqueous solution methyl green,	125

Add

Water,	300
Absolute alcohol,	200
Glycerin,	100

These mixtures stain the red corpuscles orange, the nuclei bluish-green, the eosinophile granules red (acid fuchsin), the neutrophilic granules purple, and the basophilic granules green. Heated specimens or those fixed by placing them in absolute alcohol and ether for a considerable length of time (twelve hours) give the best results.

Various modifications of these mixtures have been suggested, but individual experience must govern such alterations. In my own work I have, as a rule, found larger quantities of methyl green necessary. Simpler combinations, such as methyl green and acid fuchsin, stain the neutrophile granules very well, but the triacid mixture gives more pleasing results.

Demonstration of Karyokinesis.—Müller's method is perhaps the most satisfactory. The heated specimen is placed in concentrated aqueous solution of picric acid for twenty-four hours, washed in running water for several hours, and then stained for twelve or twenty-four hours in very dilute hæmatoxylon solution (Delafield's) or for a short time in undiluted borax or ammonium carmine. If the hæmatoxylon specimens are overstained they should be treated hastily with one-half or one-per-cent. HCl in weak alcohol.

Demonstration of Corpuscular Degenerations.—The mixtures of eosin and hæmatoxylon or methyl blue already referred to are sufficient to demonstrate the condition of the red corpuscles known as *polychromatophilia*. The nature of this condition is discussed in another place; for the present it suffices to say that the normal red corpuscle fixed by heat or chemical agents is monochromatophilic, taking but one color (acid) from a mixture. With progressive degenerative changes there is a tendency towards basic affinity, and in certain conditions the corpuscles take a mixture of stains. Thus with methyl blue and eosin the normal erythrocyte stains bright red; the abnormal, purplish.

Foà has described certain granular degenerations of the red cor-

puscles which are demonstrated in the following way: The blood is spread quickly upon cover-glasses, dried in air, and fixed by drawing the glass through a Bunsen flame three times. The specimen is then stained with concentrated alcoholic solution of methyl blue, washed, dried, cleared in clove oil, and mounted in xylol balsam.

Neusser has recently described certain perinuclear basophilic granulations in the white corpuscles as evidences of nuclear disintegration. These are demonstrated by preparing the blood upon cover-glasses and staining with the following, a slightly modified Ehrlich's triacid mixture:

Saturated aqueous solution of acid fuchsin,	50
Saturated aqueous solution of orange G,	70
Saturated aqueous solution of methyl green,	80
Distilled water,	150
Absolute alcohol,	80
Glycerin,	20

Glycogen may be demonstrated in the white corpuscles by staining with iodine after the method of Gabritchewski. The specimen dried in air is treated with—

Iodine,	1
Potassium iodide,	3
Distilled water,	100
Gum arabic,	excess.

After the specimen has been stained a few minutes it is examined. The cells containing glycogen present a mahogany-red color.

Demonstration of Malarial or Other Micro-organisms.—The cover-glass preparations may be fixed by heat or Nikiforoff's mixture. They may be stained with any of the eosin-methyl blue combinations. Plehn has suggested a formula containing a little alkali.

Saturated aqueous solution methyl blue,	60 c.c.
Eosin, one-half-per-cent. solution in seventy-five-per-cent. alcohol,	20 c.c.
Distilled water,	40 c.c.
Potassium hydrate (twenty-per-cent. solution),	12 gtt.

This stains the red corpuscles red, the malarial organisms blue. I have found similar stains fairly satisfactory for filaria. Bacteria are stained by the well-known methods of the bacteriologists, but many forms may be recognized by the simple blood stains. Canon's mixture, referred to before, was specially useful in this author's work on influenza bacilli.

PATHOLOGICAL CHANGES IN THE BLOOD.

Plethora.

Plethora was the term applied by the older writers to conditions in which the total quantity of blood was supposed to be excessive. This view rested entirely upon clinical observation and speculation. Experimental evidence of recent date shows that it is not possible to produce a lasting increase in the total amount of blood, though there are still certain pathological and clinical facts which seem to favor the belief that transient or continuous excess of blood may occur. The older writers distinguished several forms of plethora.

Plethora vera, or true polyæmia, was the term applied to increase in the entire quantity of blood without change in the quality. Such a condition was supposed to occur in persons living in luxury, and particularly those indulging in a generous table. Persons of this kind are still spoken of as full-blooded, and the term has a descriptive usefulness in designating robust individuals with high color and vigorous circulation. The redness of the face and mucous membranes, the injection of superficial blood vessels, the large frames and thick necks of such individuals are characteristic. Vigorous pulsations of the vessels, cardiac palpitations, dyspnœa, and a tendency to bleeding from the nose or other mucous surfaces are among the oft-described symptoms. Very often this condition is found to occur in numbers of individuals in the same family.

Plethora apocoptica or *plethora ad spatium,* on the contrary, does not represent an actual increase in the total amount of blood but rather a relative excess resulting from local anæmias, as in the application of an Esmarch bandage, after amputation of a limb, or the like.

Plethora hydræmica seu serosa was regarded as a condition in which the total quantity of blood is increased by addition of water. In consequence the blood becomes of poorer quality though increased in quantity. Such a condition was regarded as a frequent disorder of the blood after hemorrhages, in cachectic conditions, and the like.

Other forms of plethora of transient character were described but were considered to be of comparatively little importance. The unlikelihood of plethora existing as a permanent condition has been abundantly proved by experimental investigations. The subject, however, is still exceedingly difficult of solution on account of the unsatisfactory character of all of the methods of determining the total quantity of blood. In experiments, however, in which large quantities of liquid have been administered and the amount of water sub-

sequently eliminated has been determined it has become clear that the economy soon frees itself of the liquid absorbed. v. Lesser and Worm-Müller tried to produce experimental plethora by transfusion of blood into healthy animals. These experiments showed that while there was a temporary increase of pressure after the injections, the intravascular tension soon decreased and the number of corpuscles in a given quantity of blood increased, showing a disappearance of liquid from the circulation. Subsequently the number of corpuscles decreased and the normal relations were soon re-established. Worm-Müller held that half of the blood plasma injected leaves the blood-vessels within a very few hours, and the polycythæmia thus developed is also of short duration. Basing his views upon these experiments, Cohnheim denied the possibility of plethora, and many authorities are disposed to admit this view without question. Nevertheless clinical and pathological evidence has been cited by Oertel, Bollinger, and others to prove the possibility of plethora in the original sense. The most important point in favor of the view is the cardiac hypertrophy and dilated condition of the vessels in beer-drinkers, but this does not warrant immediate deductions. Beer-drinkers doubtless suffer with constantly repeated dilutions of the blood, each of which is soon counterbalanced by active renal functions, sweating, and the like. Each attack of this kind taxes the cardiac power and, as in laborers, miners, etc., cardiac hypertrophy results from overwork. There is therefore no certain evidence presented by this observation of actual plethora.

As for the symptoms of plethora as they were described, it is altogether probable that these are manifestations resulting from disturbance of the vasomotor system rather than from increased quantities of blood. In the experiments referred to no symptoms of like character occurred even during the period immediately following the transfusion of blood, though the quantity of blood injected amounted to the entire bulk of the animal's blood. Only after injection of half again as much as pre-existed did disturbances and death of the animal result.

The less important forms, plethora hydræmica and plethora apocoptica, must likewise be looked upon as supposititious rather than real conditions. In cachectic conditions and after hemorrhages there is certainly no evidence to warrant the assumption that the blood mass is increased above the normal by the addition of water; and in cases of increase in the relative quantity of blood by compression of a certain vascular area the elimination of water doubtless soon decreases the amount of liquid to the normal.

Oligæmia.

Oligæmia, or a decreased quantity of blood, occurs after hemorrhage. There is little evidence to show that a lasting form of true oligæmia, in which the quantity of blood is diminished without disturbance of its quality, may occur. The older writers distinguished such a condition as *oligæmia sicca* in contradistinction from *oligæmia serosa*, in which the amount of blood was supposed to be decreased at the same time that the quality was reduced. It seems likely, that in some of the forms of chronic symptomatic anæmia there may be a reduction in the quantity as well as in the quality of the blood. This thought is suggested in many cases of profound cachexia, as in carcinoma, but methods are wanting to prove the truth or untruth of the assumption.

The oligæmia following hemorrhage may lead to death when the loss of blood has been excessive. The loss of blood which may be sustained without a fatal result is, however, often surprisingly large. Finally the quantity is reduced so greatly that the circulation fails and death occurs after convulsions or coma. When smaller quantities of blood have been lost, the volume is soon equalized by absorption of fluid from the tissues. This leads to a hydræmic condition, though not to hydræmic plethora; and the final restoration of the quality of the blood occurs more or less slowly, according to the amount of hemorrhage.

Hydræmia and Anhydræmia.

Experimental and clinical evidence shows that there is an intimate relation between the tissues and the blood, in that the amount of the latter is quickly regulated by the addition of fluid in cases in which the mass of the blood has been reduced, and an abstraction where excess of liquid has occurred in the blood. Thus the immediate effects of hemorrhage (oligæmia = reduction of the volume of the blood) or of excessive consumption of water are soon obviated and the total amount of circulating blood is kept within quite narrow limits. Temporarily the blood may contain a relative excess (hydræmia) or diminution (anhydræmia) of the watery constituent.

Hydræmia may occur directly in consequence of excessive consumption of water. The specific gravity of the blood may be notably reduced, but the excretion of liquid soon restores the condition of the blood. A hydræmic state of the blood may be due to vasomotor conditions leading to dilatations of the blood-vessels. Thus it has

been found after section of vasomotor nerve trunks and in consequence of vascular dilatation due to external heat, the administration of nitrite of amyl, and similar causes. A more lasting hydræmic state occurs in consequence of hemorrhage in which the volume of the blood is restored by a passage of liquids from the tissues into the blood. Gradually the processes of hæmogenesis restore the normal relations.

Anhydræmia.—Loss of fluid by diarrhœa or excessive sweating, may occasion considerable inspissation of the blood. This has long been recognized in cholera. The quantity of red corpuscles is relatively increased, the number sometimes reaching six or seven millions per cubic millimetre. The specific gravity and the amount of solid residue increase in accordance with the degree of inspissation. Experimentally Czerny and others have shown that the condition of the blood may be profoundly influenced by excessive sweating. The absolute quantity of blood is greatly reduced in these experiments, but the relative amount in comparison with the body weight does not alter materially, showing again the close relation of the total liquid of the tissues and that of the blood. Vasomotor influences exercise a similar effect. Thus cold baths may occasion a rapid though transient inspissation of the blood, partly no doubt the result of contraction of the vessels and expression of liquid. Injections of tuberculin and other substances have a like effect, causing a decrease of the water in the blood, as do the so-called lymphagogues of Heidenhain.

The clinical results of anhydræmia are still somewhat questionable. The older writers assumed that many of the symptoms in the algid stage of cholera are directly due to inspissation of the blood, the circulation failing on account of the mechanical difficulties offered by the thickened blood. The experiments of Czerny, however, would seem to indicate that the narcosis and other manifestations observed in cases of maximum anhydræmia are rather the consequence of chemical changes and intoxication of the central nervous system.

Coagulation.

Blood after its removal from the body tends to undergo a process of solidification—coagulation or clotting. This process consists in the formation of a solid portion (clot) which afterwards contracts and expels a light-colored fluid—the serum. The clot when it is first formed is bright red in color and consists of a mass of fibrin, usually in the form of a fibrillar network, entangling the red blood corpuscles. Later when contraction has occurred, the color becomes darker from condensation. Occasionally the upper layer of a clot is very light in

color. This has been termed the "buffy coat," or from its occurrence in blood in inflammatory conditions, the "crusta phlogistica." It is due to the unusually rapid subsidence of the red corpuscles or to the retardation of coagulation in consequence of which the red corpuscles have time to sink. The same phenomena may be produced by delaying the coagulation by putting the blood in a cool place.

Nature of Coagulation.—The essential feature of coagulation is the formation of fibrin. This is a light-colored or whitish body, having remarkable elasticity and a tendency to form threads or fibrils. In a thoroughly dried condition it is granular. It is insoluble in water, but when exposed for a long time to solutions of sodium chloride or when acted upon by proteolytic ferments it dissolves, with the formation of two globulins. Subsequently albumoses and peptone are formed.

The study of the physiological or chemical processes of coagulation has been pursued with great zeal by a long list of investigators, but it is to Alexander Schmidt and his pupils that the greatest credit is due for the discovery of certain essential facts. The first of these is that the antecedent of fibrin exists only in the blood plasma. The separation of the fibrin itself takes place only under the influence of other substances, mainly derived from destruction of cells—notably leucocytes. This view, first expressed by Montegazza, is now quite generally believed.

If blood plasma is obtained in a pure state, free of corpuscles, by sedimentation at 0° C. and filtration, this does not coagulate spontaneously; at least it remains liquid for a considerable time. The antecedents of fibrin are, however, contained in it and coagulation is rapidly produced by the addition of watery extracts of leucocytes, or of various other cells, including red corpuscles, muscle cells, lymphadenoid cells, etc. The same result follows from the addition of cellular extracts to liquid transudates which are not themselves spontaneously coagulable. The substance of the plasma or liquid transudates, which becomes converted into fibrin, is an albuminous body known as *fibrinogen*. This substance forms fibrin only in the presence of *calcium salts* and of a *fibrin ferment;* but other substances (paraglobulin, etc.) supposed by some to be essential, are in no sense necessary to the process. The necessity of the calcium salts is shown by the absence of coagulation in liquids in which the addition of soluble oxalates has removed the calcium salts from solution; and the absence of fibrin formation when pure fibrinogen and fibrin ferment are brought together in the absence of calcium. Recent investigations (Lilienfeld and others) show that fibrin is a calcium compound of a substance occurring in the plasma and known as *thrombosin*. In

the separation of the latter the fibrinogen is broken up and the calcium compound of thrombosin or fibrin is formed, while at the same time another albumin, the *fibringlobulin* is produced.

The nature of the fibrin ferment is as yet a matter of considerable difference of opinion. Investigators are, however, quite unanimous in regarding the white blood corpuscles as the important source of the ferment, though other cells may furnish a part. According to Schmidt the leucocytes contain two substances, *prothrombin* and a *zymoplastic* substance, the combination of which occurs when the leucocytes are destroyed. The resulting compound is the *fibrin ferment*.

Recent investigations have shown that fibrin (in the presence of calcium) or thrombosin (in the absence of calcium) may be formed from fibrinogen by acids of various kinds, including the nucleinic acid of the nucleohiston (tissue fibrinogen). This indicates a further source of substances capable of promoting coagulation, but this element as a rule is unimportant.

The amount of fibrin in blood clots is amazingly small in comparison with the size of the coagulum. It rarely exceeds 0.1 to 0.4 per cent. of the total weight of the blood.

The rapidity of clotting in health varies somewhat with the time at which it is determined, the activity of the physiological processes, etc., but the variation is slight. In most cases the period elapsing from the time the blood is drawn until a clot is formed is 2.5 minutes in normal men, according to Wright; but others have found the limits to be from two to ten or twelve minutes. It is of course difficult to establish the exact time when the coagulation may be said to have begun or ended; and the results obtained by different methods are not entirely comparable.

Clinical Relations of Coagulation.—In health the blood shows no tendency to coagulate in the vessels, and the capillary blood remains fluid after death. Changes, however, in the blood or in the circulation lead to a more or less pronounced tendency to clotting. Any foreign body introduced into the blood current furnishes a place for the leucocytes to attach themselves and to undergo disintegration. Thrombosis or fibrin formation is the invariable result. The same thing is observed in diseases affecting the walls of the blood-vessels, as in atheroma, aneurysm, arteritis, endocarditis, etc. In these cases more or less pronounced thrombosis is usually observed and is the result of the arrest of leucocytes and their destruction. The fibrin formation in such cases is analogous to that which occurs in case of traumatic injury of the blood-vessels (ligature). Spontaneous coagulation may occur when hæmolytic agents cause destruction of blood

corpuscles. Experimentally this is found in various intoxications, such as those with pyrogallic acid, chlorate of potassium, etc., and it is found in certain diseases in which toxic substances circulate in the blood (jaundice, nephritis, pernicious anæmia). In the infectious diseases coagulability varies. At times the rapidity is increased, in other cases decreased, and the amount of fibrin factors may vary in the same way. In hæmophilia and the hemorrhagic diseases generally and in leukæmia the coagulability of the blood would seem to be decreased. The terms *hyperinosis* and *hypinosis*, used to designate excess and diminution of fibrin factors, have less clinical significance than was formerly attributed to them.

Lipæmia.

Fat is an invariable constituent of the normal blood, but is present more abundantly at certain times than others. It is particularly abundant during the process of digestion when oil droplets may be discovered here and there under the microscope. The nature of these is recognized by their high refractive power and by the black color given to them by osmic acid. In pathological conditions the quantity of fat may vary from the physiological amount to that in which the field of the microscope is literally filled with small or large droplets and in which the naked-eye appearance of the blood is very markedly altered. The plasma in such cases may become opalescent or even quite opaque and the blood itself may present an unusually light color, while the fat accumulates upon the surface on standing. Among the conditions in which lipæmia has been met with are pulmonary tuberculosis, chronic nephritis, diabetes, asphyxia, and certain forms of intoxication, notably alcoholism. The explanation has been given in these cases that the accumulation of fat is due to arrest of the processes of oxidation, but this explanation is not applicable to all cases. Doubtless alteration in the digestive function may play a part, while a direct entrance of fat from the adipose tissues, as in fat embolism is, an occasional cause.

Melanæmia.

This condition is characterized by the appearance of dark granular matter in the blood and is readily distinguished by microscopic examination. It does not constitute an independent disease, but is a symptomatic condition, occurring in certain forms of malaria and much more rarely in relapsing fever or other diseases. In its typical form it is met with only in the severe forms of tropical malaria.

The pigment occurs in the form of yellowish, brown, or black granules, or as small rod-like particles either in the plasma or enclosed in leucocytes. Sometimes there are granular masses of free pigment or a leucocyte may be so densely filled that it presents a similar appearance. The free granular masses are held together by a hyaline albuminous substance. Doubtless malarial plasmodia have often been mistaken for pigmented leucocytes by the older writers.

The amount of pigment is usually small in mild cases of malaria, but in some of the malignant forms the microscopic picture is most striking, every field presenting an abundance of free granular matter or pigment-laden leucocytes. At the same time the blood is found to be greatly deteriorated in correspondence with the amount of corpuscular destruction, from which the melanæmic condition directly results.

Leucocytosis.

Synonyms.—Polycythæmia alba; hyperleucocytosis.

Definition.—The term leucocytosis is applied to a more or less transient increase in the number of leucocytes mainly involving the polymorphous neutrophilic forms. This definition, however, does not apply in all cases. Sometimes leucocytosis is a continuous or chronic affection, as in cases of malignant tumors or chronic infections; and, on the other hand, there are instances in which the increased number of leucocytes does not affect the polynuclear so much as the mononuclear elements. Such cases, however, are exceptional, and in general the definition given is fairly descriptive and serves to distinguish the condition from leukæmia, in which there is constant and essential increase of the leucocytes, always affecting the mononuclear elements to a greater extent than the polymorphous cells.

Pathogenesis.

The nature of leucocytosis has occasioned considerable discussion, and the views regarding the causation have been greatly at variance. The older writers, notably Virchow, held that the increased number of leucocytes results from the stimulation of the blood-making organs and the consequent overproduction of leucocytes. Added to this there was supposed to be a retardation of the conversion of the white into red corpuscles. This view, however, is rarely entertained at the present time, and there is little evidence in its favor. Karyokinesis of the leucocytes of the circulating blood and of the cells of the blood-making organs has been demonstrated only occasionally and in slight degree, and is rarely, if ever, any distinct evidence of pro-

ductive processes in the lymphatic organs. Hoffmeister, however, claims to have found a marked leucocytic infiltration of the intestinal walls during the period of digestive leucocytosis. This infiltration affected not only the adenoid tissues, but the interglanduiar portions of the mucosa, and seemed to him to be due to karyokinetic activity.

Joas and Löwit have offered the theory that leucocytosis is in a manner a regenerative or hyperplastic process preceded by diminution in the number of leucocytes. This theory has been particularly defended by Löwit, who has found that the leucocytosis caused by the injection of bacterial products and various organic substances is always preceded by a decreased number of leucocytes—*leucopenia*. This latter condition he ascribes to destruction of leucocytes (*leucolysis*), and he holds that it is essential to the subsequent leucocytosis, although the manner in which the preliminary decrease in leucocytes or their destruction brings about the subsequent leucocytosis is not explained. This theory of leucocytosis cannot, however, be entertained, since it has been shown on the one hand that excessive destruction of leucocytes does not occur in the preliminary stages, and that in the second place injection of certain substances (glycerin extract of spleen, Goldscheider and Jakob) will cause a leucocytosis without preliminary hypoleucocytosis or leucopenia.

The theories which at the present day are received with most credence are those which ascribe the condition to chemotatic influences. Buchner and Römer believe that the cause of the phenomena resides in the bacterial proteins, substances derived from the body of the bacteria, rather than to toxins produced by the micro-organisms. Most observers, however, look upon the toxins of micro-organisms and upon metabolic products as the active agents which cause increase in the number of circulating leucocytes. Buchner and Römer held that the proteins exercise a double influence, one formative and one chemotatic. In consequence of the former of these there is an increased number of the leucocytes resulting from direct or amitotic division in the blood-making organs or venous channels (Römer), while the latter influence leads to an increase in the number of white cells in the circulating blood as the result of the attractive influence exercised upon the free leucocytes within the blood-making organs. Ehrlich contends that the phenomena of leucocytosis result from activity of the bone marrow in converting the abundant mononuclear into polymorphous leucocytes.

In contradistinction to these theories may be placed those which have been advanced in recent years and which explain the phenomena of leucocytosis upon the assumption of disturbed relations in the circulation of the leucocytes or of chemotaxis without actual increase

in the number of white corpuscles. Schulz, in his investigations of this subject, was led to believe that the phenomena of leucocytosis are entirely due to altered distribution, so that increased numbers in the peripheral circulation may be taken as an indication of decreased numbers in the interior of the body, or the reverse. He could find no evidence either of destruction of the leucocytes (the *leucolysis* of Löwit) or of absolute increase in the number of leucocytes coming from the blood-making organs. V. Limbeck explains the phenomena of leucocytosis entirely upon the theory of chemotaxis, and points to the close relationship of this condition with inflammatory exudation. Leucocytosis, however, may occur without exudations and the processes are not essentially related, although it is undoubtedly true that the underlying processes, in either case, have much in common.

The theory which at the present day seems most acceptable is that of Goldscheider and Jakob. These observers show that injections of bacterial products, of organic extracts, and various albumins cause a preliminary decrease in the number of leucocytes—hypoleucocytosis, followed by a more or less pronounced increase—hyperleucocytosis. The more powerful the injection the more pronounced the preliminary hypoleucocytosis and also the secondary hyperleucocytosis. The action of the substances injected is a double one, at first repellant upon the lucocytes and causing their arrest in the capillaries, particularly of the lung; and secondly, attractive upon the blood-forming organs, causing an increased output of leucocytes already formed, or perhaps a new formation of leucocytes with discharge into the circulation. When small doses of the substances are injected there is a preliminary hypoleucocytosis due to the repellant action, and a secondary hyperleucocytosis as soon as the substance injected has become disseminated in the fluids of the body. When moderate-sized doses are injected the primary repellant action is more pronounced, but the attractive influence coming on when the poison has become diluted is also more marked. In case of enormous doses the repellant action is exceedingly marked, but at the same time the irritative and attractive influence upon the blood-making organs is immediate and pronounced, so that there is at once a decided output of leucocytes. The repellant influence may continue sufficiently to cause arrest of the newly added leucocytes in the capillaries of the lung or other parts for a time, but the continuous addition from the blood-making organs soon determines decided leucocytosis. The development of leucocytosis without preliminary hypoleucocytosis is explained by the assumption that small doses of the poisonous substances distributed throughout the circulating fluid are not sufficiently repellant to produce retention in the capillaries, while, on the other

hand, by repetition the attractive influence upon the blood-making organs gradually serves to increase the number of leucocytes in the circulating blood. In other words, the equilibrium between the processes of repulsion and attraction is disturbed in favor of attraction.

It is unnecessary to dwell upon the experimental evidence in favor of the chemotatic theory of leucocytosis, and in particular that which has been adduced to prove the reliability of the views just expressed. That there is a preliminary disturbance of the distribution of leucocytes in the circulation, such as was maintained by Schulz, has been shown by numerous investigators, and that the arrest of leucocytosis is mainly in the capillaries of the lung seems to be definitely established. The subsequent increase of leucocytes in the general circulation does not, however, seem entirely dependent upon a reversal of the conditions with the appearance of the leucocytes in the peripheral and their disappearance in the central channels, since Goldscheider and Jakob were able to demonstrate an equal and indeed an increased number of white cells in the pulmonary capillaries during the stage of hyperleucocytosis. From this fact alone it would seem probable that the secondary increase is due to an output from the blood-making organs and possibly also to actual multiplication of leucocytes in these structures.

Of the truth of the latter statement, however, little can be said. It rests almost entirely upon speculation. Undoubtedly if a vigorous attractive influence is exercised upon the lymphatic organs and extrusion of leucocytes results, it would seem likely that formative influences would at the same time be set into operation; but direct proof of this is wanting.

Certain facts point to the production of leucocytes in other tissues than the blood-making organs. Among the indications pointing in this direction may be cited the observations of Hoffmeister on the intestinal infiltrations during digestion, the increase of eosinophilous cells in asthmatic sputa and in local inflammatory exudations. Weiss in particular insists upon the local origin of leucocytes and their entrance into the circulation; but upon the whole it is far more likely that these views will be disproved by further studies.

The theory of chemotaxis serve in almost every particular to explain the phenomena of leucocytosis as they have been observed in physiological and pathological conditions. Active multiplication of the leucocytes probably occurs as a secondary though important part of the process, but this remains to be proved.

The Blood in Leucocytosis.

The increased number of leucocytes varies greatly according to the nature of the underlying condition. The variability in the number of leucocytes in health makes it somewhat difficult to establish an absolute limit beyond which the number of leucocytes may be considered abnormal; but, roughly speaking, it may be said that when the number per cubic millimetre exceeds 10,000, the condition is one of leucocytosis. The percentage proportions of leucocytes as compared with the red corpuscles are of comparatively little value, since the proportion is altered as much by increase or decrease of the red corpuscle as by change in the number of leucocytes. In moderate leucocytosis the number increases to 20,000 or 30,000; in marked cases to 40,000 or 50,000, but the number may exceed the latter figure considerably in certain cases. No fixed rule can be established for the liability to increase of leucocytes in different individuals under similar conditions; but children generally show a more marked increase than adults.

In the great majority of cases the increase affects the polymorphous neutrophilic forms rather than the mononuclear elements. The proportion of these forms may be increased from the normal (65 to 75 per cent.) to 80 and 85 per cent., or even greater numbers. In one of my cases (suppurative meningitis) I found 99.5 per cent. of all the leucocytes polymorphous and neutrophilic. Sometimes the conditions are reversed and instead of an excess of polymorphous cells the mononuclear elements are increased. This is particularly common in cases of lymphosarcoma or leucocytosis due to other malignant diseases, in instances of terminal leucocytosis and in the post-hemorrhagic forms. In some of these cases I have found the mononuclear elements considerably in excess of the polymorphous forms, and may cite in illustration a recent case following hemorrhage in which the proportions were as follows: Polymorphous, 43.5 per cent.; lymphocytes, 27.1 per cent.; large mononuclear (large lymphocytes?), 16.4 per cent.; transitional, 10 per cent.; and eosinophile (polynuclear), 2.8 per cent.

Similar, though perhaps less striking, instances are not uncommon in the other conditions named; while in the leucocytosis of early childhood the large proportion of mononuclear elements is usually striking. This is especially well marked in certain cases of rachitis, syphilis, and the condition termed by v. Jaksch infantile pseudoleukæmia.

Occasionally markzellen or myelocytes have been found and karyokinetic figures have been observed by a few investigators.

Etiology.

The *clinical causes* of leucocytosis are extremely numerous; it may occur during health as well as in various diseases. The forms of physiological leucocytosis are those which occur in the new-born, in pregnant women, and after the ingestion of food.

Leucocytosis of the New-Born.—This has been observed by a number of authors, and has been ascribed to inspissation of the blood as well as to the continuous or protracted effect of digestion. As a rule, the number of leucocytes is not markedly increased, though from 15,000 to 20,000 per cubic millimetre are frequently noted. During the first year of life the number declines and by the second year has usually reached the adult proportion. The mononuclear forms, especially lymphocytes, are more abundant, according to Rieder, than the polynuclear elements. This has also been observed by other investigators.

The *leucocytosis of pregnancy* is not invariable, though it occurs in a considerable proportion of cases. Among 31 investigated by Rieder 21 presented distinct increase of the leucocytes, the average number being 13,000 per cubic millimetre. At the end of pregnancy the number rapidly decreases and soon reaches the normal.

Digestive leucocytosis has been recognized for a long time, observations having been recorded by Nasse, Moleschott, and Virchow. It is quite frequently observed, though not invariably, and occurs within a few hours after the meals, reaching its maximum in three or four hours and gradually disappearing in six or eight. Proteid food is more striking in its effects than is a mixed diet. In cases of prolonged abstinence from food there may be a decrease in the number of leucocytes, as Luciani found in the studies of the Italian faster Succi, in whom the number of leucocytes sank to 861 per cubic millimetre after the first week. Subsequently there was a slight increase (1,530 per cubic millimetre), lasting until the termination of the thirty days' fast.

Digestive leucocytosis occurs in persons suffering with gastro-intestinal disease as well as in health, excepting cases of gastric carcinoma, in which, according to the investigations of Müller and Schneyer, there is constant absence of this phenomenon.

Among the causes of pathological leucocytosis may be included various inflammatory and infectious processes, cachectic conditions, malignant new growths, hemorrhage, and toxic agents or drugs.

Inflammatory and Infectious Leucocytosis.—In nearly all of the infectious diseases which have been examined there has been found a more or less pronounced increase in the number of leucocytes, the

prominent exceptions to this rule being tuberculosis, typhoid fever, malaria, influenza, and lepra.

Croupous pneumonia generally shows a decided increase, beginning with the elevation of temperature and continuing until the decline of the fever, when the number of leucocytes usually decreases rapidly. The polynuclear elements are particularly conspicuous, while the eosinophilic cells as a rule are exceedingly few in number. Numerous observations have been recorded to show that unusually virulent cases may be distinguished by the absence of this leucocytosis, which therefore becomes significant in a prognostic sense. Pseudo-crises are not attended with decline of the number of leucocytes and may be thus distinguished from the actual crisis. The extent of pulmonary involvement does not bear a direct relation to the degree of leucocytosis, which seems on the contrary to be dependent upon the virulence of the infective material.

Streptococcus Infections.—In cases of streptococcus infection there is usually a more or less decided increase in the number of leucocytes, as is seen in cases of cellulitis, erysipelas, puerperal sepsis, or secondary streptococcic infection in cases of pulmonary tuberculosis and other chronic diseases. The degree of leucocytosis is generally moderate and corresponds somewhat in its variation with the temperature curve.

Staphylococcus Infections.—Suppurative inflammations in any part of the body are usually attended by a moderate increase in the number of leucocytes and the presence of pus may be thus detected. In a number of cases of suppurative appendicitis in which the staphylococcus albus was discovered I found the number of leucocytes to vary from 15,000 to 40,000, while in non-suppurative cases the leucocytosis was extremely moderate or absent. Similar observations may be made in cases of staphylococcus suppuration occurring in other localities.

Inflammations of the serous membranes, peritoneum, pleura, and meninges are frequently attended by moderate leucocytosis and there is undoubtedly, as v. Limbeck holds, a certain relation between the cellular richness of the exudate and the degree of leucocytosis. The latter is practically always present in inflammations of these structures dependent upon infection with streptococci, staphylococci, or pneumococci; but in tuberculous inflammations the number of leucocytes is not increased. I have found a like increase of leucocytes in acute endocarditis of malignant type and in all of these cases the polymorphous elements predominate greatly.

Acute Infectious Fevers.—Moderate leucocytosis has been found in acute rheumatism, diphtheria, variola, scarlatina, and anthrax. It

has been discovered occasionally in measles, though as a rule the number is not increased in this condition. In small-pox the number of leucocytes, according to the investigations of Pick, bears a distinct relation to the character of the eruption, being practically normal during the earlier stage of the infection, but considerably above the normal when suppuration has begun.

Cachetic leucocytosis may occur in a great variety of conditions. Among these congenital syphilis and rachitis hold important rank. In either of these considerable increase may be observed and sometimes the leucocytosis is so pronounced that authors have at times hesitated to exclude leukæmia, the difficulty of diagnosis being not a little increased by the frequency of mononuclear leucocytosis in such cases and by the enlargement of the spleen and glands.

Agonal leucocytosis or the terminal leucocytosis developing towards the end of life in various chronic affections is in a measure an exaggerated form of cachectic leucocytosis. At times it becomes very pronounced. It has been repeatedly discovered in cases of pernicious anæmia, but occurs in various diseases. The explanation of this condition, in part at least, may be the reduction of blood pressure and the discharge of the leucocytes from the lymphatic organs into the circulation. This explanation, however, does not suffice in all cases. In some instances terminal infection may play a part. The mononuclear elements and in particular the small lymphocytes are often increased more strikingly than the polymorphous elements. This, however, is not invariably the case.

Malignant Tumors.—The leucocytosis associated with malignant growths is particularly frequent in cases of sarcoma. In such cases the number may vary from the normal to fifty thousand or more, and it may be difficult in some cases of sarcoma involving the lymphatic apparatus to draw a sharp dividing line between symptomatic leucocytosis and leukæmia, as in all cases of sarcoma the mononuclear elements tend to increase more particularly than the polynuclear. Leucocytosis is less frequent in carcinoma, though it occurs in a certain proportion of cases, particularly in the later stages when the bone marrow has become involved. The mononuclear elements may be conspicuous as in sarcoma and certain investigators have called particular attention to the presence of large mononuclear forms or myelocytes.

Post-hemorrhagic leucocytosis occurs after large or small losses of blood, usually appearing within a short time and continuing for several days, according to its original severity. The explanation given by the older writers, and still occasionally repeated, that this is due to the adhesive property of the leucocytes and their attaching

themselves to the sides of the blood-vessel walls cannot be accepted. It is more likely that the reduction of blood pressure leads to the discharge of leucocytes from the tissues of the body and lymphatic system into the circulation. The proportion of lymphocytes may be strikingly increased, as occurred in a recent case already referred to, in which the lymphocytes constituted 27.1 per cent., and the large mononuclear and transitional forms, which were undoubtedly closely allied to the lymphocytes, 16.4 per cent and 10 per cent. of the total number.

Mechanical and Thermal Causes.—Leucocytosis after massage and after cold baths bears a resemblance in its causation to the last-named form. The experiments of Mitchell showed a decided leucocytosis in four cases out of ten in which massage was practised, and moderate increase in three, while the number remained normal in the other three. The studies of Winternitz and Thayer have shown a quite constant increase in the number of leucocytes following cold bathing in health or in disease (typhoid fever). The general stimulation of the circulation by massage or the application of cold would seem to be operative in such cases by causing a return to the circulation of leucocytes stagnant in various parts of the body.

Medicinal Leucocytosis.—Reference has already been made in the discussion of the nature of this condition to the increase of leucocytosis produced by injection of various toxic substances. Among those which have been employed in therapeutics are: pilocarpine, oil of turpentine, oil of cinnamon, peppermint, tuberculin, camphor, urea, and certain organic extracts as those of the spleen, thymus, and bone marrow. Various other organic substances and bacterial toxins have been found to exercise a similar influence in experimental investigations.

Leucocytosis is of no importance as a clinical condition and there are no symptoms directly attributable to it.

Hypoleucocytosis.

Synonyms.—Leucopenia; aleucocytosis.

Definition.—The term hypoleucocytosis is used to designate decrease in the number of leucocytes. In clinical studies it is somewhat difficult to establish a number which shall represent the lowest limit that may be considered normal. Arbitrarily, however, we may fix upon the number six thousand. In experimental investigations, on the other hand, it is easy to establish the existence of hypoleucocytosis by the previous examinations of the blood and by the acute character of the condition.

Hypoleucocytosis has been the subject of investigation of a number of recent experimenters, and its study has served to clear a number of difficulties in the way of a proper interpretation of the nature of leucocytosis. The term leucopenia, indicating poverty of leucocytes, was introduced by Löwit, who holds that the decreased number of leucocytes is the result of increased destruction. Objection may, however, be made to both the term and the view expressed; for it is likely from other experiments that there is no actual poverty of leucocytes, and proof is wholly wanting that the leucocytes are destroyed more rapidly than in health. The explanation of hypoleucocytosis of Schulz and of Goldscheider and Jakob is simple and convincing. These observers found, after injection of various toxic substances, that the capillaries of the internal organs, notably the lungs, become overfilled with leucocytes at the same time that the peripheral circulation shows decreased numbers. Of the truth of this assertion there can be no doubt at all, though difference of opinion may still be justified regarding the proper explanation of the phenomenon noted. Experimental hypoleucocytosis is usually followed by increased numbers of leucocytes or hyperleucocytosis.

In human pathology hypoleucocytosis has as yet occupied but little attention. It occurs in certain cases of tuberculosis, typhoid fever, malaria, pneumonia, and in some instances of cachexia, starvation, and the like. The decreased number of leucocytes, or at least the absence of leucocytosis, met with in cases of pure tuberculosis (without secondary infections) is of great diagnostic value in certain cases. In particular the differential diagnosis between tuberculous and simple inflammatory affections of the serous membranes is sometimes greatly facilitated by this fact. The same may be said of the absence of leucocytosis in typhoid fever. In these diseases the number of leucocytes may be entirely normal, actual decrease in the number occurring in only a small proportion of cases. The character of the leucocytes usually shows no striking variation from the normal, though a preponderance of mononuclear elements has been observed by some investigators in typhoid fever and an almost complete absence of eosinophilous forms in tuberculosis by others.

The normal number of leucocytes or even hypoleucocytosis may be met with in certain cases of pneumonia. This is principally important from the fact that such cases have been found more serious in prognosis than cases in which the usual leucocytosis is observed.

The decrease in the number of the leucocytes occurring in various chronic symptomatic anæmias, in cases of malnutrition and the like, is devoid of clinical significance. In cases of toxic or infectious hypoleucocytosis it is not unlikely that the massing of the leucocytes

in the capillaries of the lungs may help in the production of the respiratory symptoms and complications of such cases.

Polycythæmia.

Synonyms.—Polycythæmia rubra; erythrocytosis.

This condition may be either actual or relative, and it is difficult to determine in how far the increased number per cubic millimetre is dependent upon actual increase in the quantity of corpuscles in the entire blood or upon decreased quantity of plasma. Polycythæmia occurs normally in the new-born, the figures having already been referred to. A temporary increase in the corpuscles may be produced by transfusion of blood, but this increase is soon removed by the process of cytolysis. The influence of climate is of considerable interest. Viault observed that his blood showed 5,000,000 red corpuscles at Lima, while after fourteen days' stay in the Cordilleras the number increased to 7,000,000, and after three weeks to 8,000,000. Subsequently this subject has been studied by a number of observers who have invariably found increased numbers at elevated stations. A table has been constructed by Wolff and expanded by Jaruntowski and Schroeder, showing the increasing number of corpuscles with increased altitude. This table is as follows:

Location.	Observer.	Altitude in metres.	Number of corpuscles.
Christiania	Laache	Sea level	4,970,000
Göttingen	Schafer	148	5,225,000
Tübingen	Reinert	314	5,322,000
Zürich	Stierlin	414	5,752,000
Auerbach, i. V.	Wolff	400 to 450	5,748,000
Goerbersdorf	Jaruntowski and Schroeder	561	5,800,000
Reiboldsgrün, i. V.	Wolff	700	5,970,000
Arosa	Egger	1,800	7,000,000
Cordilleras	Viault	4,392	8,000,000

A similar effect is observed in consequence of circulatory disturbances, a number of observers having determined the increased number of corpuscles occurring in conditions of failing circulation and particularly when cyanosis is present. In such cases the number of corpuscles may be increased to 6,000,000, 7,000,000, or even greater numbers. Rapid loss of serum in cases of cholera, diarrhœa, excessive sweating, or the like, similarly increases the number of corpuscles in a given quantity of blood.

The explanation of these conditions is somewhat difficult. In the case of elevated regions it has been held by some that the increased

demand for oxygen-carrying substances leads to multiplication of the number of corpuscles, while others have maintained that there is a loss of liquid by the increased respiratory activity. Objections might, however, be made to either of these explanations, though perhaps each of them contains some element of truth. The increased activity of the circulation in elevated regions undoubtedly serves in a measure to produce the result noted by bringing into the circulation all of the available corpuscles from the tissues, and the effect of massage in increasing the number of red corpuscles (Mitchell) and the effect of cold baths (Winternitz and others) point in the same direction.

In the case of cardiac disease stagnation of the circulation and the retention of the corpuscular elements in the periphery undoubtedly play a part. There seems little reason for believing that the increased numbers of corpuscles are dependent, as some have held, upon fragmentation for the purpose of furnishing greater oxygenating surface, and the view recently expressed that the polycythæmia of high altitudes is due to increase of the length of life of the corpuscle is interesting but unconvincing.

Clinically, polycythæmia is without significance, and the fact that its development in persons who have taken up their residence at a high altitude and its subsequent disappearance when they return to sea-level are marked by no disturbance of health is a strong point against the assumption that there is on the one hand rapid production of corpuscles or on the other hand subsequent cytolysis.

ANÆMIA.

The most important of the alterations of the blood are the conditions grouped under the name anæmia (*α*, priv., and *αἷμα*, blood). This term in its etymological and older sense was used to designate poverty in blood or bloodlessness. This view of anæmia has been long since abandoned, and it is recognized that anæmia as it is met with clinically represents a variety of affections in which deterioration of the blood may occur in one or another of several particulars. Absolute reduction in the volume of blood does undoubtedly occur in certain cases, and the term "oligæmia" is properly applicable, but even in such cases the depreciated quality of the blood is more important. The intimate relationship existing between the circulating medium and the liquid of the various tissues allows a ready exchange of fluid in one direction or the other, so that the mass of the blood is kept at approximately the same bulk.

Deterioration in the quality of the blood may occur in the follow-

ing directions: Reduction of the number of red corpuscles, or *oligocythæmia,* is one of the most frequent and most striking alterations in the various anæmic conditions. This very rarely occurs without a simultaneous change in the chemical constitution of the serum; but the latter may be relatively unimportant. The number of corpuscles may be normal while the hæmoglobin is reduced in amount. Such a condition (*oligochromæmia*) is not infrequently observed in chlorosis and other conditions. Otto first called attention to the fact that after hemorrhages the regeneration of blood always effects an increase to the normal in the number of corpuscles before the hæmoglobin has reached the normal. Oligochromæmia is therefore in a sense a regeneration phenomenon, and certain authors would regard it as such in all cases. This view must not, however, be too readily received. Undoubtedly there are cases in which the reduction of hæmoglobin is the primary condition. Finally the blood may be reduced in quality by the diminution of albuminous constituents or by the addition of water. These changes are usually coincident and probably always associated with changes in the quantity of hæmoglobin or the number of corpuscles. It is improper, in view of the above considerations, to substitute the term oligocythæmia for the older clinical name anæmia, and though the latter cannot now be used in its older and literal sense it is useful to designate a group of affections characterized by deterioration of the blood.

Reference may be made at this point to *pseudo-anæmia.* It is very well known that certain individuals, and often a number of individuals of the same family, present marked pallor without exhibiting any evidence of anæmia in a clinical way or upon the most careful examination of the blood. This pallor may be due to abnormalities in the capillary supply of the skin, to deficiency of the normal pigment, or to other causes. Sometimes pallor develops suddenly or gradually in persons in whom examination of the blood shows no deficiency in color or in the number of corpuscles. The explanation of such cases is found in the study of the general circulation. Sahli found among the causes of such "apparent anæmia" reduction in blood pressure with consequent deficiency of circulation in the skin. In other cases disturbances of the vasomotor system doubtless play a part, as in the instances reported by Winternitz as "anæmia spuria acutissima." In these instances there is a sudden or gradual accumulation of blood in the interior with reduction of the amount customarily present in the skin. The consequence of this is an anæmic appearance without actual anæmia. Undoubtedly, however, vasomotor disturbances of this kind frequently cause interchange of liquid from the tissues to the blood or the reverse, and alterations in

the character of the blood may follow. These alterations, however, may be trifling or absent, or they may be slowly developed so that in the mean time the paradoxical change of color without discoverable change in the blood is observed.

Classification of the Anæmias.

Various schemes have been suggested for the classification of the anæmic affections, but none of these has proved entirely satisfactory. The earliest classifications were the purely clinical ones based upon the more striking features of groups of cases. In this manner pernicious anæmia was distinguished from the general body of the anæmias by Addison, and chlorosis by still earlier authorities. Subsequently the attempt was made to divide all cases into two groups: representing first the cases in which the anæmia is secondary to some other affection or symptomatic of such; and second, the cases in which the disease of the blood is primary, originating in the blood itself or in disorders of the blood-making organs. This was undoubtedly a progressive step, though recent knowledge does not support the arbitrary limits established by the classification. Disorder of blood formation or of hæmolysis doubtless plays as great a part in certain of the so-called secondary anæmias as in the primary forms; but the classification is still useful for practical purposes. We must, however, modify somewhat our conceptions of the meaning of the terms.

By primary, idiopathic, or essential anæmias we may designate a group of diseases in which the striking manifestations are those affecting the blood, the blood-making organs or both, and in which the other symptoms are subsidiary or dependent upon these conditions. It is by no means improbable that many of these cases are dependent upon organic diseases, which careful investigation may reveal; the essential point is rather that the condition of the blood and hæmatopoietic organs is the dominating clinical feature. In pernicious anæmia, in leukæmia, and in Hodgkin's disease there are undoubtedly cases in which disorders of the gastrointestinal tract precede the anæmic disorder and bring it about; while in chlorosis the same view has been largely entertained. In none of these cases, however, does the primary disease play a conspicuous part in the clinical phenomena.

Among the diseases of this group are chlorosis, progressive pernicious anæmia, leukæmia, and Hodgkin's disease. Certain authors still distinguish a form of *simple primary anæmia*, but there are no characters by which this may be satisfactorily recognized. The

cases spoken of as *splenic anæmia* are widely different in nature, some belonging properly among the symptomatic anæmias, others being cases of Hodgkin's disease.

The terms *symptomatic* or *secondary anæmia* may be applied to the cases in which deterioration of the blood occurs as a consequence of various diseases, but in which the anæmia remains a subordinate condition. In this group are the anæmias attending gastrointestinal, cardiac, renal, hepatic, and other organic diseases; those following acute or chronic infections of various kinds; the anæmias due to nutritional diseases, to parasites, or various intoxications, and the anæmia of hemorrhage. The last named in a measure forms a separate group, but in its manifestations resembles the symptomatic anæmias very closely and may therefore be included among the latter.

The attempts to classify anæmias on a purely anatomical or pathological basis, distinguishing those in which oligocythæmia, hydræmia, oligochromæmia, or other features are conspicuous, have been entirely useless in practical or scientific considerations of the subject; and the hope of determining in which cases hæmogenesis is at fault and in which abnormal hæmolysis has thus far proved illusive.

Symptomatic Anæmia.

Etiology.

The causes which occasion symptomatic anæmia may be classified in a number of groups, including unfavorable sanitary conditions, hemorrhage, parasites, infectious diseases, intoxications, organic diseases, and new growths.

Surroundings, Diet, etc.—The surroundings of patients exercise a more or less pronounced influence upon the condition of the blood as upon the general health. Whatever influences tend to cause deterioration of the latter tend also to produce an anæmic condition.

The effect of diet is difficult to determine, as the experimental evidence and some of the investigations made upon persons undergoing prolonged fasts have been quite at variance in their results. Senator and Luciani found that the blood of the Italian fasters Cetti and Succi did not undergo the deterioration that might be expected, and experiments upon animals have sometimes shown considerable increase in the number of corpuscles instead of decrease. It must be remembered, however, that in such instances the increased number of corpuscles is probably to a large extent apparent, being due to inspissation of the blood from the loss of liquid from the body. The

experiments upon animals would seem to show that fasting in itself affects the general blood mass in equal proportion with the body weight, and that deterioration of the quality of the blood does not occur (v. Hösslin). When the blood is decidedly affected this is probably due to secondary or associated conditions, such as fever, organic disturbances, etc. Continuous bad food, however, is usually associated with other debilitating influences and undoubtedly leads to anæmia, as is seen in the inhabitants of besieged cities or in times of famine.

Occupations which are exacting and lead to a greater output than income of energy occasion similar results. Residents of tropical climates frequently present a strikingly anæmic appearance, particularly when they have recently arrived in such climates, but to a large extent this appearance is deceptive, being probably due to vasomotor conditions rather than to a condition of the blood itself. The actual anæmias of the tropics are dependent upon definite and specific causes.

Hemorrhage may occasion moderate or intense anæmia, according to its causes. In cases of traumatism with rupture of a large vessel, in instances of hemorrhages from the stomach or the intestinal tract, after hemorrhages from the lungs or uterus, or in cases of loss of blood occurring from superficial carcinomata or other tumors, the degree of anæmia is sometimes intense. The same may be said of the hemorrhages occurring in the so-called hemorrhagic diseases hæmophilia, scurvy, or purpura. In instances in which the loss of blood is extremely gradual, the resulting anæmia is correspondingly slow in development. Among the cases of this kind may be noted hemorrhoids, hemorrhages from the gastrointestinal mucosa due to obstructions in the portal circulation, and new growths affecting the mucous surfaces. The loss of a large quantity of blood may be immediately fatal, though the exact amount which must be lost in order to to produce such a result is difficult to determine and probably varies greatly in different individuals. In animals a loss of three per cent. of the body weight causes an immediate depression of the blood pressure, but this loss is rapidly regained. This equalization results from the action of the vasomotor mechanism as well as from the absorption of fluid from the tissues. The primary result of hemorrhage must always be a reduction of the total amount of blood or oligæmia, so that the blood count taken immediately after the hemorrhage may show no evidence of anæmia. When the secondary equalization, however, occurs and the fluid of the tissues is absorbed by the capillaries a progressive deterioration of the blood by dilution ensues. It is not, however, until some hours after the hemorrhage that the anæmia reaches its maxi-

mum. In most instances of severe but not extreme hemorrhage the number of corpuscles sinks to 3,000,000 or at most 2,000,000 per cubic millimetre and the hæmoglobin to approximately equal proportions, although there is usually here as in other forms of symptomatic anæmia a greater reduction of coloring matter than of blood cells. The specific gravity of the blood decreases and the amount of solid residue falls below the normal. In extreme hemorrhagic anæmias the number of corpuscles may sink below 1,000,000, as in a recent case under my own observation of hæmatemesis due to cirrhosis of the liver in which the number of red corpuscles was 800,000 and the hæmoglobin fourteen per cent. of the normal. The red corpuscles usually show striking variations in size, and nucleated corpuscles are more or less abundant, the smaller forms or normoblasts as a rule predominating greatly. The white corpuscles are usually increased (see Leucocytosis) and the blood plaques may be very numerous.

Chemically the blood shows decrease of albuminous matter (hypalbuminosis, Schmidt) and increase of saline constituents, notably phosphate and chloride of sodium. The regeneration of the blood after hemorrhages may be rapid, but is usually quite slow in cases in which the loss of blood has been considerable, the typical conditions of regeneration being apparent, viz., comparatively rapid increase of corpuscles and slow augmentation of the hæmoglobin. The actual time consumed in the regeneration varies greatly in different individuals. The recovery from a single hemorrhage may occur in a few days or a week or not for three or four or even six or seven weeks.

Parasites.—Various forms of parasitic anæmia have been recognized. The malarial organism is an example of direct parasitic invasion, in which the anæmia is largely due to the multiplication of the organism within the blood or circulation and the consequent destruction or consumption of corpuscles. In another group of cases the parasites occupy the gastrointestinal tract and produce anæmia indirectly. Among this group are Ankylostomum duodenale, Bothriocephalus latus, Anguilula intestinalis, and less frequently various forms of Tænia, Ascaris lumbricoides, and even the Oxyuris vermicularis. The flukeworms Distoma pulmonalis and Distoma hæmatobium, and the Filaria sanguinis hominis may indirectly occasion anæmia by hemorrhage or the disease dependent upon their invasion. The most intense anæmias are those occasioned by the ankylostomum and bothriocephalus. In the case of the former of these it has been held that the loss of blood directly occasioned by the parasite is the cause of the anæmia. This view, however, may be doubted, since intense anæmia may occur in instances in

which the number of parasites is very inconsiderable. On the other hand, large numbers of ankylostoma may cause no anæmia at all. Further, the character of the anæmia is often unlike that met with in cases of manifest post-hemorrhagic anæmia and analogy drawn from the anæmic conditions due to other parasites or gastrointestinal diseases leads to the conviction that the anæmia of ankylostomiasis is not post-hemorrhagic in character. In the case of the bothriocephalus there is no loss of blood at all and the anæmia may be quite as intense as in cases of ankylostomiasis. Recently the opinion has gained ground and seems justified that these parasites cause anæmia by direct interference with the digestive process or by the formation of poisons either directly or in consequence of disease or decompositions of the parasite itself. The milder grades of anæmia are doubtless due to disturbances of the gastrointestinal functions and to diarrhœa. The Megastoma entericum, the amœbæ, and the monadines among the lower parasitic forms may occasion considerable anæmia by their direct effect upon the mucous membrane (gastrointestinal catarrh, ulceration, hemorrhages).

Infectious Diseases.—Both the acute and chronic infections are prone to cause deterioration of the blood, this being probably due to direct action of the micro-organisms, as is undoubtedly the case in malaria, or to the hæmolytic or globulicidal effect of toxins or other substances arising in the course of infectious diseases. During the progress of the disease anæmia may not be marked, and indeed the number of corpuscles is not rarely normal or even increased beyond the normal. This may be accounted for by the fact that disturbance in the distribution of water within the economy leads to inspissation of the blood. A decided point in favor of this view is the almost invariable occurrence of more or less anæmia after the subsidence of the disease. The degree of anæmia is rarely intense, though it may become quite marked in the severer forms of disease, such as scarlatina, rheumatism, and pyæmia. In malaria the anæmia may be rapidly developed and severe; after typhoid fever and pneumonia the degree is usually moderate.

More pronounced anæmias are met with in the chronic infections. In cases of syphilis during the secondary stage there is sometimes a considerable degree of reduction of the hæmoglobin without a corresponding reduction in the number of corpuscles. This fact was first pointed out by Ricord, but has subsequently been confirmed by numerous observers. It is true not only of the secondary stage but also of tertiary syphilis, though in the latter the chloroanæmic type is less frequently pronounced.

In congenital syphilis the degree of anæmia is often very marked,

the blood presenting appearances at times like those of chlorosis or at other times like those of pernicious anæmia. The red corpuscles may be decidedly altered in shape and size and nucleated forms may be abundant. The number of leucocytes is frequently increased and sometimes notably so. Differential counts of the leucocytes sometimes show a preponderance of the mononuclear forms, and myelocytes and leucocytes containing basophilic granulations have been observed. Chronic malaria may give rise to intense anæmia and a general appearance of cachexia. The number of corpuscles and the amount of hæmoglobin are greatly reduced and pigment particles may be observed in the plasma or leucocytes (see Melanæmia).

The anæmia of tuberculosis and particularly that of the pulmonary form, varies considerably in character and intensity. There may be extreme anæmia due to the tuberculous intoxication alone, but in most instances the associated changes with the consequent disturbances of organic functions and secondary infections play a part in the determination of the anæmia observed. In the case of pulmonary tuberculosis the earlier stage when the primary infection has occurred may be marked by a moderate degree of anæmia of chloroanæmic type. Subsequently the character of the blood may be practically normal, but in the last stages when softening and cavity formation with secondary infection have occurred the condition of the blood may again suffer considerably and leucocytosis which is usually absent in the earlier stages, may be observed.

Toxic Anæmia.—Various intoxications arising within the body or conveyed from the exterior may occasion anæmic conditions of the blood. To a large extent the anæmias of infections or of gastrointestinal and nutritional disease are due to the action of poisons developed within the body; and it is likely that autointoxication plays a more important part in the development of certain severe anæmias, notably pernicious anæmia, than has hitherto been believed. In Addison's disease and in myxœdema there may be considerable anæmia, which in these cases is probably dependent upon the action of toxic substances allowed to circulate within the body instead of being neutralized or destroyed. Poisons introduced into the system from without may act as direct hæmolytic agents, or as causes of disturbance to the functions of various organs, so as to produce anæmia. Experimentally certain substances, such as pyrogallol, aniline, nitrobenzol, and chromic acid, have been found to be capable of producing intense anæmia by direct action, while chronic plumbism or poisoning by mercury, zinc, copper, and other metallic substances may occasion high grades of anæmia more or less indirectly by their effects upon the gastrointestinal tract or upon other organs.

Organic Diseases and New Growths.—Among the organic diseases which may occasion anæmia, the gastrointestinal disorders are prominent. In either acute or chronic catarrh of the stomach or intestines there may be moderate or even severe anæmia, according to the intensity of the process. Anæmias of this description are particularly common in children, in whom they may reach the highest grades, *anæmia gravis*. In some of these instances marked leucocytosis may be associated. The association of atrophy of the gastric and intestinal mucous membrane with anæmia will be more particularly considered in the discussion of pernicious anæmia. The pathogenesis of these forms of anæmia has occasioned considerable discussion, and it is likely that autointoxication plays an important part. In gastric ulcer and in carcinoma of the stomach or intestines the anæmia may become severe, especially in instances in which hemorrhages have occurred. The type of the anæmia in these conditions is usually marked by the excess of the reduction of hæmoglobin over that of the corpuscles; but the number of red corpuscles is usually more strikingly affected than in true chlorosis and the disproportion between corpuscles and hæmoglobin accordingly less marked. This is seen from the average of three instances of advanced anæmia due to gastric carcinoma in which I found the number of corpuscles to be 2,890,000 (fifty-seven per cent.). In one case of gastric carcinoma under my observation the examination of the blood showed the typical features of pernicious anæmia, and the same condition has been observed by others.

Hepatic disorders rarely occasion severe anæmia, though in cases of abscess and intense jaundice dependent upon biliary obstructions or hypertrophic cirrhosis a considerable degree of anæmia may occur. Experimentally bile is known to have globulicidal properties, and in severe jaundice a tendency to hemorrhage is not infrequently observed.

Circulatory disease may be attended with marked anæmia, though the majority of instances present little deterioration of the blood and the number of corpuscles may be actually above the normal. In congenital cardiac disease with cyanosis, the number of corpuscles may reach 8,000,000 per cubic millimetre, and in any case loss of compensation may lead to a similar though less marked increase in the number of corpuscles. When the compensation is permanently disturbed there is usually a more or less hydræmic state of the blood or the examination may show no evidence of anæmia. In my own experience the most striking anæmia occurs in cases of aortic regurgitation. In aortic stenosis the patient's appearance is frequently deceptive, the pallor being due rather to vasomotor conditions than

to an actual state of the blood. Acute cardiac affections (endocarditis, pericarditis) influence the blood as the acute infectious diseases.

In renal disease the appearance of the patient is often deceptive, the condition of the blood being frequently normal or nearly normal despite extreme pallor. This is particularly true of parenchymatous nephritis. Marked anæmia may, however, occur in acute or chronic cases in which the loss of blood and albumin through the kidneys is considerable, and in cases of chronic interstitial nephritis in the later stages. In one instance of the last-named variety under my observation there was extreme reduction of the hæmoglobin (twenty to twenty-five per cent.) and of the corpuscles (forty per cent.) with moderate jaundice and other evidences of intense anæmia. The chemical alterations of the blood in nephritis, and particularly in uræmia, have not been satisfactorily determined. There is undoubtedly an increase of urea and of potassium salts in some instances and the uric acid or other constituents of the blood may be augmented. The corpuscles themselves show the characters met with in other anæmias. The occurrence of myelocytes has been occasionally noted.

Certain nervous diseases, such as chorea, spinal degenerations, or dementia, may be attended by anæmia, but the latter is rarely marked.

The chronic nutritional diseases, osteomalacia, rickets, gout, obesity, diabetes, myxœdema, and Addison's disease may be accompanied by more or less anæmia, but this is rarely marked excepting in the case of rickets. Rachitic children often present intense anæmia, partly the result of the general disease and partly no doubt the consequence of gastrointestinal complications. The number of the corpuscles has frequently been found below 1,500,000 and may sink to 500,000. The corpuscles themselves present marked alterations in size and form, and nucleated red corpuscles are abundant. Augmentation of the white corpuscles is quite frequent and may reach marked proportions.

Malignant tumors occasion more or less anæmia, according to their situation and according to the occurrence or the absence of hemorrhage. Carcinoma of the pylorus with or without hemorrhage and uterine cancer attended with hemorrhage lead to the most pronounced forms of anæmia. Not rarely this is of the pseudochlorotic type, as has already been pointed out. The corpuscles present no characteristic feature, though the occurrence of leucocytosis with predominance of mononuclear forms may be met with in either sarcoma or carcinoma, and the presence of myelocytes has been urged as an evidence of metastasis to the bone marrow in cases of cancer. Chemically, the presence of notable quantities of sugar in the blood is significant as indicating carcinoma.

The Condition of the Blood.

The state of the blood in the symptomatic anæmias is dependent upon the degree of the anæmia more than upon the underlying cause. Minor differences have been alluded to in the review of the various conditions with which anæmia is associated, but the more important features must be considered further. In all cases there is a reduction in the amount of hæmoglobin which progresses more or less regularly and which may reach extremely high grades in severe cases. In ordinary instances the proportion determined by Fleischl's hæmometer varies from 60 to 70 or 75 per cent.; in severe cases it falls to 40 or 50 per cent., and sometimes the amount may be reduced to 15 or 20 per cent. Taking blood examinations of one hundred consecutive cases of gastric, intestinal, cardiac, nervous, pulmonary, and intestinal diseases in which a certain degree of pallor led to examination of the blood, I found the average percentage of hæmoglobin to be 74; but among these cases there were a number in which the proportion was far below the average, some of them being as low as 30 or 40 per cent. of the normal. The number of corpuscles does not decrease as greatly as does the proportion of hæmoglobin, and in many instances the corpuscular richness is actually normal or even above the normal. Formerly it was held by some that symptomatic anæmias are characterized by an equal reduction in the number of corpuscles and in the percentage of hæmoglobin. This, however, as has just been stated, is incorrect, the rule being that the hæmoglobin suffers greater reduction than the corpuscles. The disproportion, however, in most instances is only slight, as may be seen from the fact that in the average of the hundred cases alluded to, the proportions were 88.6 per cent. (corpuscles) and 76.4 per cent. (hæmoglobin). There are numerous instances, however, in which the disproportion is as great as that met with in typical cases of chlorosis, such instances occurring with particular frequency in cases of tuberculosis, syphilis, rickets, and carcinoma. These cases have been appropriately termed chloroanæmia.

The individual red corpuscles vary considerably from the normal. In most instances in which the anæmia is at all severe irregularity in the size of the corpuscles is striking, and the small forms or microcytes may be quite abundant. The large forms or megalocytes are less frequently met with, though they are not particularly uncommon in severe cases; and nucleated erythrocytes are met with in the severest forms of symptomatic anæmia, especially in those which have developed rapidly. In post-hemorrhagic anæmia they may

form a striking feature; and they are particularly abundant in the anæmias of young children, being rarely absent in cases of even ordinary grade in children below the age of five. The small forms or normoblasts are most abundant, but the larger forms (megaloblasts) are not unusual. Mitotic figures or fragmentation of the nuclei of the red corpuscles may sometimes be observed, especially in children. Degenerative changes of the protoplasm of the red corpuscles have been described by various authors, paricularly the condition known as polychromatophilia, in which the corpuscles become stained purplish by mixtures of eosin and hæmatoxylon or methyl blue instead of assuming the single color (pink) characteristic of the normal red cell. Other variations, such as the slighter degenerative changes of Maragliano, may be observed, but the significance of these is somewhat doubtful.

Herz, Kraus, and others have recently contributed investigations which would indicate that the red corpuscles at times undergo a more or less uniform swelling, probably dependent upon hydropic conditions, and of acute or chronic character, according to the nature and cause of the anæmia. The former observer found acute swelling of the corpuscles in typhoid fever and peritonitis, and after hæmoptysis; among the causes of chronic swelling of the corpuscles were various forms of cachectic anæmia.

The leucocytes may present no variation from the normal, or, on the other hand, may be increased in number. Very rarely they are decreased below the normal. In the toxic and infectious varieties of symptomatic anæmia there is usually a moderate leucocytosis, while in the more chronic cachectic conditions (notably malignant tumors) there may be a continuous and sometimes considerable increase in the number of leucocytes. In such cases the differential count may also show variations from the normal, the mononuclear elements, particularly the small lymphocytes, tending to become more numerous.

Chemical Changes.—The most important alterations of the composition of the blood in symptomatic anæmias are the decrease in albumin and the increase in the amount of water. Both of these alterations correspond with the reduction in the specific gravity. The alkalinity of the blood is usually diminished, though it may be normal and is never decidedly altered. The saline constituents, particularly the potassium and sodium, are of particular interest, nearly all recent observers having found that there is a uniform diminution in the quantity of potassium and an increase in the amount of sodium. The increased amount of the latter substance was first pointed out by Becquerel and Rodier and subsequently by a number of authors. Recently the subject has been studied with great care by Biernacki,

and it is evident from his observations as well as from those of others that the increased amount of sodium is commensurate with the increased hydræmia of the blood.

As a rule the quantity of potassium decreases in correspondence with the increase of sodium chloride and corresponds with the reduction in number of the corpuscles.

The phosphoric acid of the blood, according to Biernacki, is usually reduced, though other observers have found it increased.

The amount of iron discovered by chemical analysis does not always correspond to the apparent reductions determined by estimations of the hæmoglobin. Becquerel and Rodier and other chemical investigators found the quantity reduced in anæmia, but Biernacki, though he has substantiated these results in a measure, has found that the reduction is only trivial in many cases and that in comparison with the solid matter of the blood in general, it is often increased.

Symptoms.

The symptoms in the case of symptomatic anæmias are often slight and may be entirely independent of the condition of blood.

The general appearance of the patient is more or less characteristic. The skin grows more and more pallid until in severe cases it presents a deathly whiteness. In other cases it is yellowish or grayish and unhealthy in appearance, while dusky rings may be noted about the eyes. Occasionally there is a distinct icteric hue, as in pernicious anæmia, but this is rarely marked. No opinion can be formed of the degree of anæmia, nor indeed even of its existence by this pallor. In some persons there is an habitual light color of the skin which is easily mistaken for anæmia if this fact is not borne in mind, and on the other hand there are individuals in whom the color of the cheeks, lips, and other mucous membrane is constantly vivid despite the existence of considerable anæmia. The same may be said of the conjunctivæ.

Emaciation is usually present in moderate degree, but is for the most part dependent upon the underlying causes of the anæmia rather than upon the condition of the blood itself. Subcutaneous œdema may be noted about the ankles, especially towards night, or when the patient has been active beyond his strength. Puffiness of the eyelids or of the cellular tissues beneath the eyes may occur and sometimes there is extensive anasarca. The latter, however, is quite rare.

The skin is usually dry and often quite harsh. On the contrary

it is occasionally noted that the patient perspires more freely than normally and copious sweats may occasionally occur.

Gastrointestinal disorders are extremely common. One of the earliest symptoms is usually failure of appetite with or without decided disturbances of digestion. The tongue is coated and the breath is usually heavy. Constipation may prove a most troublesome symptom, while in rare instances there is a tendency to periodic attacks of diarrhœa.

Circulatory disturbances may mark the onset of the symptoms and are usually prominent throughout the course of the case. The heart action is rapid and the pulse weaker than normal. Physical examination may determine some enlargement of the cardiac chambers, and anæmic murmurs may be heard at the base of the heart and in the vessels of the neck. These, however, are much less frequent than in cases of chlorosis or pernicious anæmia. The most striking symptom is palpitation, which occurs in nearly all cases in which anæmia is decided, coming on with every exertion or on slight emotional disturbance. In the later stages the cardiac power may fail very greatly in consequence of cardiac dilatation, and the dropsy previously existing from the anæmic condition of the blood becomes greatly augmented. Serous effusions may sometimes occur in the internal cavities.

The general condition of the patient is one of more or less pronounced depression. He complains of growing weakness and of constant languor. Very commonly the sleep is disturbed by unpleasant dreams or the patient may be entirely sleepless. On the other hand, there are instances in which the patient rouses himself with difficulty from the tendency to continuous somnolence. Ringing in the ears, vertigo, and a proneness to syncopal attacks give evidence of a deficiency of the cerebral circulation; while the failure of peripheral circulation is denoted by complaint of cold feet and hands, or of a tendency to take cold on slight exposure.

Neuralgic disturbances are very common, and the statement of Romberg that neuralgia is a cry of the nerves for better blood receives a certain justification from the frequency of these conditions in anæmic persons. The underlying diseases, however, rather than the disorder of the blood, are frequently the cause of these symptoms. Headache is a common symptom and may be dependent upon the anæmia alone or upon gastrointestinal disturbances occurring in consequence of the anæmia. In children it may prove a distressing symptom and the cause may easily be overlooked.

Acute post-hemorrhagic anæmia is marked by sudden pallor, with failing circulation, dyspnœa, and a tendency to syncope and uncon-

sciousness. If the hemorrhage is slight these symptoms are transient, but when severe losses of blood have been sustained they may increase in severity and continue to a fatal issue. In cases in which repeated slight hemorrhages have occurred the patient grows more and more pallid, and not rarely presents a somewhat yellowish color of the skin and conjunctivæ. The circulation becomes feeble, and the pulse, though often quite full, is usually easily compressible; puffiness or actual œdema is not unusual.

The urine is, as a rule, normal, though the saline constituents and the urea are often reduced in amount. The color may be lighter than normal and the quantity of the urine is not rarely increased. The latter is particularly true of cases in which secondary nervous manifestations are developed. In such instances there may at times be decided excess in the amount of urine secreted. Slight albuminuria is sometimes met with, but casts are unusual, and actual nephritis very rarely develops in consequence of the anæmia itself.

Disorders of the respiration of a serious character are unusual, but dyspnœa is very commonly met with and may be pronounced. In some cases there is a harassing dry cough, while in others actual bronchitis is observed.

Severe manifestations, such as hemorrhage, are rarely met with in symptomatic anæmias, though occasionally epistaxis may occur from time to time, and in unusual instances more serious hemorrhages may take place (hæmatemesis, hæmoptysis, hæmaturia).

Menstrual disorders are very frequent, particularly in women approaching the climacteric; the most common are dysmenorrhœa and scanty menses, but occasionally profuse bleeding may be noted.

Course and Prognosis.

The course and prognosis of symptomatic anæmias depend entirely upon the underlying cause. Left to itself the condition of the blood may grow steadily worse until high grades of deterioration are witnessed; but very rarely does this become sufficiently marked to constitute a serious danger.

Diagnosis.

The recognition of anæmia is always easy. Sometimes, however, it is difficult to distinguish between symptomatic anæmias and the so-called primary anæmias, particularly chlorosis and pernicious anæmia.

Attention has been called in the discussion of the etiology to the diseases in which the blood assumes a chlorotic character. The diag-

nosis in such cases cannot be made by an examination of the blood alone. It is only after a careful scrutiny of the onset of the disease and its course, together with a minute examination of the possible causes of secondary anæmia, that the latter may be excluded and the condition be recognized as one of true chlorosis. The occurrence of the latter condition in young girls and its association with distinct menstrual disorders aid greatly in the recognition of this disease, and the diagnosis of chlorosis at other ages or in the male subject cannot be made without the most careful consideration of the patient's history and general condition.

Pernicious anæmia is less commonly simulated by symptomatic anæmias. I have, however, seen instances in which the resemblance was most striking, and it is undoubtedly true that many of the cases of so-called pernicious anæmia in early life have been merely instances of intense secondary anæmia. The condition of the blood is so characteristic in pernicious anæmia that this alone suffices in most instances to establish the diagnosis. In the rare instances, however, in which high grades of microcythæmia, macrocythæmia, and poikilocythæmia occur in secondary anæmias and in which nucleated corpuscles are met with, the general condition of the patient and the clinical course of the disease, together with the evidences of definite underlying diseases obtained in the physical examination, must be considered in making the diagnosis.

It was formerly held that the blood in the symptomatic anæmias differs from that of chlorosis or pernicious anæmia in showing an equal reduction of hæmoglobin and red corpuscles. From what has been already stated regarding this matter it will be seen that such a view cannot now be entertained. Indeed, it is more common to find an excessive reduction of hæmoglobin than a diminution of equal pace with the diminution in the number of red corpuscles; and in some instances excessive oligocythæmia may occur with comparatively moderate reduction of the coloring matter.

Treatment.

The management of anæmia in itself must always take second rank to the treatment of the underlying affections. In some cases, however, when the latter is obstinate and uncontrollable, treatment directed to the condition of the blood may be valuable despite the disease which has occasioned the anæmia, and by improving the state of the blood may render efforts towards controlling the original disease more successful. Among the remedies of greatest usefulness, iron and arsenic easily take the first place. Iron may be adminis-

tered in the forms in which it is used in the treatment of chlorosis and the details will be considered in that place. Among the more useful forms are Blaud's pills, the tincture of the chloride of iron, reduced iron, and some of the vegetable salts such as the oxalate, malate, or ammoniocitrate. Not rarely it is advantageous to combine stomachics or general tonics such as gentian, nux vomica, or quinine; and constipation must always be obviated by the occasional use of saline aperients. Combinations of rhubarb or aloes with iron are of particular advantage in instances in which the constipation tends to be obstinate. Arsenic is most frequently used in the form of Fowler's solution, given alone or in combination with iron. The addition of arseniate of potassium or sodium to Blaud's pill is advisable in all cases in which a long-standing anæmia has existed, as in cases of post-malarial cachexia.

When the patient's general condition is cachectic, nutrient and general tonic remedies in addition to iron and arsenic are employed with advantage. Among these, cod-liver oil in emulsion, and phosphorus or iodine in various forms prove useful. In anæmic and cachectic children the syrup of the iodide of iron has long enjoyed a high reputation.

Complications must be treated as they arise, but for the most part it is wise to refrain from multiplying remedies. The diet of the patient and the details of his general life require regulation in accordance with the condition which has occasioned the anæmic state. In most instances life in the open air, sunlight, and moderate exercise are advantages in the treatment which cannot be neglected.

Post-hemorrhagic anæmia is treated in the same manner as other cases when it is moderate in degree or slowly developed. In the acute cases in which the loss of blood is considerable, measures must be instituted to prevent anæmia of the brain. The patient must be kept in a horizontal position or even inverted so that the head is considerably lower than the feet; bandages may be applied to the limbs to force the blood from the periphery to the internal organs; and finally the loss of blood and depletion of the vessels may be compensated by hypodermic, intravenous, or rectal injections of saline solutions. In ordinary practice rectal enemata of hot water or saline solutions are most readily administered and the passage of the liquid into the depleted vessels occurs with great rapidity. Cardiac stimulants, such as ether, ammonia, camphorated olive oil, or strychnine, and external heat may be necessary to sustain the action of the heart; but care is to be exercised in cases in which the hemorrhage itself is at all likely to recur. After the immediate dangers of the loss of blood have subsided, iron, arsenic, and other tonic remedies are useful.

Chlorosis.

Synonyms.—Chloræmia; Chloranæmia; Febris alba; Febris seu Icterus amantium; Morbus virgineus; Fœdi virginum colores; Cachexia virginum: *Bleichsucht* (Ger.); *chlorose* (Fr.); *clorosi* (Ital.); *clorosis* (Span.); the green sickness.

Definition.—Chlorosis is a primary or essential anæmia dependent upon retarded hæmatogenesis, occurring almost exclusively in young girls or women, and characterized by peculiar pallor and evidences of anæmia and by reduction of the quantity of hæmoglobin and to a less extent of the number of corpuscles.

Anæmic conditions are occasionally met with in which the symptoms and the condition of the blood are quite similar to those observed in chlorosis, but in which the age or sex does not correspond to that usually observed, and in which there is an underlying disease which has occasioned the anæmia. Such forms of anæmia have been met with in tuberculosis, cancer, syphilis, and other affections and have been designated by the name chloroanæmia. These cases are not to be confused with chlorosis proper, and are not comprehended in the definition.

Etiology.

Two classes of causes are plainly distinguishable in the study of the etiology of this disease. In the first place we recognize certain fundamental, constitutional, or essential causes which predispose the individual to this form of disease and which alone may suffice to cause its evolution. These cases are instances of spontaneous chlorosis. Secondly, there are determining or exciting causes which may or may not occur in individual cases, but which, when present, merely serve to bring into activity the essential defects.

Among the essential causes sex, age, heredity, and certain constitutional conditions are important.

Sex.—Chlorosis is essentially a disease of the female sex, as the terms Morbus virgineus, Obstructio virginum, etc., given to it by the older writers, indicate. The disease, however, sometimes occurs in the male sex, though by no means as frequently as has been claimed by some authors. Nonat, for example, found among sixty-eight cases twenty-seven boys. Certainly this proportion is entirely erroneous, though the claim of others that the disease never occurs in the male sex is also fallacious. Hayem refers to a family in which all of the boys were affected. I have seen a single case.

Age.—Chlorosis is essentially a disease of the age of puberty. Among the cases analyzed by Immermann the onset was placed between the ages of fourteen and twenty-four years, and most writers have accepted these as the usual limits. Hayem found the average onset in fifty-two cases to be seventeen and a half years. In my own experience the age of onset has been still greater than this by a year or two. The period of onset is somewhat determined by the age at which the menstrual function begins. Thus Hayem found that it occurred about three years after the first menses. The early occurrence of menstruation (at twelve or thirteen years) before the development of the breast or pubes is usually accompanied by a tendency to the disease (Niemeyer). Chlorosis sometimes occurs in children before puberty, as in the cases of Nonat, Cantrell, Förster, and Becquerel, and sometimes it occurs in more advanced years (late chlorosis, *chlorosis tarda*).

Heredity.—Undoubtedly a strong predisposition to this disease exists in certain families. Marshall Hall, Nonat, Rech, Potain, and Dejar reported instances in which there was a direct transmission of the disease by a chlorotic mother to her daughters. Immermann has reported an instance in which all the members of a family were affected. Probably the effect of direct heredity has been exaggerated, since Hayem did not find mothers and daughters affected oftener than once in twenty cases. Nevertheless it must be admitted that there is a certain direct hereditary influence in some instances.

In addition to the direct hereditary influence it has been found that the disease very commonly occurs in association with other hereditary affections in certain families. Trousseau called attention to tuberculosis and Ashwell discussed the probability of phthisis being the consequence of chlorosis, or the reverse. Later investigation has shown a surprising frequency of tuberculous family history in this disease. Jolly found among 54 cases, 25 in which the father or mother or both had evidences of tuberculosis and 7 in which an uncle, aunt, brother, sister, or other near relative had been affected, while 8 of the patients gave evidence of the disease in their own persons. This fact has been thoroughly established by the investigations of numerous writers. Another disease with which chlorosis is related in the hereditary sense is hysteria, and other forms of nervous disease are not infrequently found recorded in the family histories (Hayem, Eichhorst).

Cancer, rickets, rheumatism, alcoholism, gout, and various other constitutional diseases have been noted, but certainly play an inferior rôle.

Constitution.—To a certain extent the constitution plays a part in

the occurrence of the disease. Not rarely it has been observed that the patients were of delicate frame and generally fragile. Wunderlich held that the disease is more common in blondes than in brunettes, but as it occurs in southern climates, as Italy, Spain, etc., with practically the same frequency as in northern countries, Wunderlich's statement is probably ill founded. All recent writers have noted no such preponderance among light-haired girls. Neither can it be said that chlorosis is essentially a disease of delicate girls, since it is sometimes met with in those of apparently robust constitution. A certain explanation of the relation of constitution to the development of this disease is furnished by the discovery of Rokitansky, Virchow, and others that there is a condition of undevelopment or hypoplasia of the heart, blood-vessels, and genital apparatus in affected persons. This, however, is by no means invariable, and sometimes there is actually hypertrophy of these parts. Nevertheless the occurrence in a certain proportion of cases in a measure explains or indicates a relation existing between the vascular and genital apparatus and the condition of the blood.

Among the auxiliary or exciting causes are many conditions affecting the environment, the habits, and general health of the individual.

Season.—Cases occur at all seasons of the year and but little influence has been apparent to most observers. Murri, however, has described cases in which the symptoms were limited to the cold months of the year, disappearing in summer. He suggests the term *chlorosis hiemalis.* Rosenbach discussed the same question before Murri and employed the term "winter chlorosis." Undoubtedly the symptoms are often exaggerated by cold.

In cases marked by relapses the latter sometimes occur regularly in the early months of the year; but in such cases close confinement during the winter, overwork at school, and like causes seem to play a part.

Distribution.—Chlorosis has been observed since the earliest times and in all parts of the world. It occurs with such frequency everywhere that it is difficult to assert that it is more common in one place than in another. Hirsch has pointed out that it is growing in frequency since the beginning of the century, and Huss has in particular called attention to the increase in frequency in Sweden.

Chlorosis affects girls living in the country as well as those of the cities, and though it has been claimed by some that the former are less prone to it than the latter the majority of authorities have found the disease quite as common in one situation as in the other.

Environment.—Undoubtedly insanitary surroundings contribute

to the occurrence of the disease, which in found very frequently among girls engaged in factories which are badly lighted and badly ventilated, and in which the work is laborious. These conditions in conjunction with insufficient or badly prepared food or a too great monotony of diet serve to bring the predisposition into operation. It must be remembered, however, that chlorosis frequently occurs in girls surrounded by luxuries and whose general life would seem to leave nothing to be desired. In these cases, however, it not infrequently happens that close scrutiny will determine causes of excessive fatigue or vices of personal hygiene, overlooked on superficial examination. Overwork at school, or the exhaustion resulting from immoderate dancing, or indulgences of other kinds may account for such cases, and the diet may be found to be grossly improper notwithstanding the surroundings of the patient.

On the other hand, sedentary habits may contribute to the development of some of the cases, and the same cause is certainly active in girls less happily situated and engaged in factories and other occupations. The lack of exercise, with poor appetite and want of fresh air and sunlight in these cases prove quite as debilitating as the fatigue of over-exertion in other cases.

Not rarely nervous impressions or influences have a powerful effect in developing the disease, and from the first writers have called attention to this class of causes. The terms *icterus amantium* and *phthisis nervosa*, *langueur*, and others are sufficiently expressive. Sauvage distinguishes among his five forms of chlorosis one which he designates as *chlorose par amour*. Immermann quotes from Ovid ("Artis Amatoriæ," Lib. I., v. 729): "Palleat omnis amans; hic est color aptus amandi!" Disappointed, unrequited, and unhappy love are frequent causes. Other forms of emotional disturbance, however, are not wanting. Sometimes sudden fright causes the rapid development of the disease, as in a girl who was startled at seeing a child fall into water and at once became cholortic. In other cases prolonged anxiety, grief, disappointment, especially when combined with physical causes of debility, are potent influences. Particular attention should be called to homesickness, a cause which is frequently seen among the servant class, and which has occasioned some of the most severe cases of the disease that have come under my notice. I would cite particularly the instance of two sisters, French girls, employed as maids, who developed the disease shortly after their arrival in America, and grew steadily worse until their return home, when immediate recovery ensued. Subsequent return to America was followed by similar results. Doubtless in such cases change of climate may exercise a certain influence.

Pre-existing Diseases.—Not rarely chlorosis develops after certain general diseases. It is not uncommon to find it in girls who have passed through severe attacks of infectious fevers or other forms of illness. Wasting diseases, particularly when prolonged, and pregnancy and lactation are occasionally noted as etiological factors. The last-named causes may determine recurrences of the disease in women who suffered with it in early girlhood, or may cause its appearance when it had never before existed.

Menstruation.—Disturbances of the menses have been recorded as of great importance in the development of the disease. It is more likely, however, that these are the result than the cause. Usually scanty or suppressed menstruation is noted, but Trousseau described instances of a menorrhagic form of the disease. It is, however, rare, and it is unlikely that the losses of blood act in any way as the primary factor, though they may contribute to further deterioration of the blood. Some instances of sudden chlorosis following suppression of the menses after their establishment have been reported, but other causes are probably operative in such cases. Further discussion of this question must be reserved for the following section on pathogenesis.

History and Pathogenesis.

The history of chlorosis is so closely connected with the theories which have been entertained regarding its nature that both may well be studied together. The disease has been recognized from the earliest times and was described with a certain amount of accuracy in Hippocrates' works treating of the affections of young girls. Subsequently descriptions of the disease were given by all of the systematic writers and the clinical history was gradually elaborated. The name chlorosis was first applied by Varandal in 1620. The watery condition of the blood was recognized as one of the essential features of the disease by Willis in 1681, and Prévost and Dumas and Denys first alluded to the decreased quantity of iron found in this disease. Juncker and Becquerel and Rodier alluded to the watery condition of the blood, looking upon hydræmia as the essential pathological condition. Cullen, and later Andral and Gavarret, noted the decreased number of the red corpuscles, while Duncan was the first to publish accurate estimations and demonstrate the decreased number of corpuscles and the reduction of coloring matter or hæmoglobin. Quinquaud further investigated the question of the quantity of hæmoglobin.

The ancient writers, beginning with Hippocrates, looked upon chlorosis as a disease in some way dependent upon disturbance of

menstruation. Hippocrates attributed it to the retention of blood in the uterus and to consequent deterioration of the general blood mass with development of the general appearances of the disease, and this view was for a long time the prevailing opinion of medical writers. Galen, Mercatus, and later Ambroise Paré and Sydenham expressed the same opinion. Lange in 1520 wrote of the disease under the name of *Morbus virgineus*, while similar titles were given it by other writers. In the present century Trousseau was a strong advocate of the theory that menstrual disturbances due to nervous disorders are important in certain cases, and Rokitansky (1846) and Virchow (1856, 1870), in describing the hypoplasia met with in the genital organs in this disease, further asserted the importance of these disturbances in the etiology of the affection. While hypoplasia of the vascular system has often been found in association with the genital hypoplasia, the latter has frequently been found without the former, and certain authors have therefore looked upon it as the more important condition. Fraenkel refers to it as a *primum movens*.

The frequent occurrence of chlorosis at the age of puberty in girls, and the almost habitual menstrual disturbances met with in the same individual have seemed to justify a certain amount of credence in these theories, but a closer scrutiny has shown that the disease is not invariably associated either with organic lesions of the kind indicated or with functional disturbances of these organs. Moreover, the undoubted occurrence of the disease in males has made it necessary to seek a further explanation of its nature.

Other symptoms frequently prominent are those manifesting themselves in various nervous disturbances, and the theory has been entertained that derangement of the nervous system is the primary and underlying pathogenic factor. Morton described it under the name of *phthisis nervosa* and Becquerel referred to it as a neurosis with secondary alterations of the blood. Trousseau says that "chlorosis should be looked upon as a nervous affection causing alterations of the blood rather than a cachexia producing disorders of the nervous system." A number of authors have described definite lesions of the nervous system, such as diseases of the sympathetic nerves, of the pneumogastric, of the spinal cord, or of other parts of the nervous system, and have built upon this various theories regarding the origin of the disease; while most writers have pointed out the effect which emotional disturbances exercise in the production of the disease. Nevertheless it is now recognized that alterations of the nervous system or functional disturbances, particularly hysteria, play no part in the etiology, excepting possibly as predisposing causes, and in many cases are doubtless entirely secondary. Very recently the

nervous theory has been in a measure revived by some who maintain that the disease is due to displacement of the abdominal organs (splanchnoptosis), causing disturbances of the abdominal sympathetic system.

A vascular theory was constructed by Virchow, and has been maintained up to the present day. The writer named pointed out that the hypoplasia of the genital apparatus discovered by Rokitansky might be wanting in the disease, while the vascular hypoplasia is quite common if not constant. In particular it was held that the hypoplasia of the heart and blood-vessels may occur without any lack of development of the genitalia, or sometimes with actual over-development, though at times with associated hypoplasia of these parts. The essential lesion was, therefore, thought to be the vascular condition. More recent investigators, however, have described cases in which the hypoplasia of the vascular system was entirely absent, and Fagge looked upon it as the result of endocarditis in childhood and as unimportant so far as chlorosis is concerned. It has been found in males without chlorosis, but in whom other and characteristic symptoms of the condition were observed (Fraentzel).

A gastrointestinal theory has been entertained in consequence of the clinical observations of dyspepsia, constipation, and other digestive symptoms, and as a result of the discovery of organic lesions in the gastrointestinal tract.

Hoffmann was the first to announce this theory, and after him Gardien, Hamilton, Bean, Duclos, and others expressed similar views. At the present day, however, the theory is most intimately associated with the name of Sir Andrew Clarke, who looked upon the affection as the result of constipation leading to the absorption of toxic products from the intestines—as a form, in other words, of autointoxication or copræmia. His belief in this view was so thoroughly grounded that he held that if a single remedy were to be administered in the treatment of the disease he would select an aperient. Stockman, however, pointed out that Clarke's aperient contained considerable quantities of iron (as much as eight grains per day) and that the clinical deductions based upon this form of treatment therefore lose in value.

Bunge and Zander have recently held to a somewhat modified theory indicating the gastrointestinal origin of the disease. According to these investigators the deficiency of hydrochloric acid in the gastric secretion and the presence of excess of sulphuretted hydrogen in the intestinal tract occasions continuous non-assimilation of iron and therefore resulting anæmia. Bunge's theory in particular has attracted attention. He held that the iron supplied to the organism is ordinarily

derived from the ferruginous nucleoalbumins of eggs, milk, and vegetables, but that in chlorosis, in consequence of abnormal intestinal putrefaction, a combination of the iron with sulphur takes place and thus progressive iron starvation ensues. He further held that the therapeutic usefulness of iron is dependent upon the fact that the iron administered enters into combination with the sulphuretted hydrogen and thus permits the iron of the nucleoalbumins to be absorbed in the normal manner. This theory, however, cannot be entertained. In the first place, it has been shown by Stockman that administration of iron in the form of the sulphide will cure the disease, while drugs quite as capable of absorbing H_2S as is iron will not effect a cure; and in the second place, the studies of Rethers and Mörner have proved that there is no increase of the aromatic sulphuric acids of the urine in chlorosis and therefore no evidence of intestinal putrefaction. Finally, the reduction of hydrochloric acid in the gastric juice which Bunge assumes in the elaboration of his theory is not constant, if indeed it be frequent; and iron is undoubtedly absorbed in other forms than as nucleoalbumins.

The theory that chlorosis is an inflammatory condition and associated with fever was a favorite one with some of the older writers, and various inflammatory lesions (of the uterus, of the intestines, and of other parts) were pointed out. Broussais applied his favorite theory of visceral irritation to the disease and attributed the phenomena of the affection to such irritation.

Finally, chlorosis has been looked upon as an affection of the blood itself. Ashwell (1838) was the first to enunciate this theory, looking upon the disease as a result of arrested development or as a failure of proper blood formation. This view has been subsequently expressed by a number of authors, notably Nonat, who regarded the disease as a result of feebleness of sanguinification. Germain Sée, Hayem, and other authors express somewhat similar views.

At the present day it is quite generally believed that chlorosis is a primary or essential blood disease dependent upon disturbance of the hæmopoietic function. Some investigators, still holding to the importance of gastrointestinal disturbances, have sought to prove that it results from intestinal intoxication and consequent blood destruction. This view, however, cannot well be maintained. Von Noorden, who has recently thoroughly investigated the subject, has sufficiently proved that evidences of increased hæmolysis are entirely wanting. It is quite generally admitted that the quantity of urobilin excreted in the urine is an indication of the quantity of destruction of blood taking place in the organism, and the light color of the urine and fæces, as well as the small quantities of urobilin

extracted with chloroform from the urine, give evidence of the insignificant amount of blood destruction occurring in the disease. In the accurate analyses of Hoppe-Seyler and A. E. Garrod urobilin was found decreased below the normal or at most in normal quantities. These results were confirmed by the investigations of v. Noorden, and according to this investigator the absence of hæmolysis is still more striking when the quantity of hydrobilin or urobilin is estimated in both the urine and fæces. Further, the examinations of the urine give no evidence of increased albuminous consumption as is the case in pernicious anæmia, malaria, and other forms of anæmia in which the evidences of hæmolysis are striking. It must be concluded from these considerations that chlorosis is not a disease resulting from blood destruction, but rather from imperfect hæmogenesis. The ultimate cause and nature of the defective hæmogenesis are as yet obscure. The occurrence of the disease in girls at an age when great demands are being made upon the general vitality, and the presence in some cases at least of evidences of imperfect development suggest that the disease is one of primary and essential weakness of the blood-making functions. This may in itself suffice to determine the development of the malady, or contributing causes, such as overwork, fatigue, nervous disturbances, and the like may be necessary to bring the underlying defect into prominence.

Pathological Anatomy.

In general it may be said that lesions of the solid tissues are exceptional rather than usual in this disease. Opportunities for pathological study are so rarely obtained that the pathology of the disease has been determined with considerable difficulty and always in cases in which death has taken place from intercurrent disease. Secondary and unessential changes have doubtless often been reported.

Changes in the Circulatory System.—More or less characteristic abnormalities have been discovered in the cardiovascular system and have been looked upon as essential in the etiology and pathogenesis of the disease. Rokitansky first called attention to the fact that the heart and the blood-vessels are frequently undeveloped, and other observers have confirmed this observation, though, despite the opinion of Virchow, it is recognized that cardiovascular hypoplasia is not invariable. The heart may be small and firm, the muscular substance and the endocardium presenting no pathological change. All of the cavities may be equally reduced in size; or, on the other hand, there may be dilatation of some of the chambers, notably the

right ventricle. The last is undoubtedly due to degenerative weakening and secondary dilatation of the wall of the ventricle. In other cases the left ventricle is also dilated and the auricles may be greatly distended. In certain cases the muscle of the heart has been found greatly diseased, small grayish-yellow spots or streaks indicating parts which have undergone fatty degeneration. This degeneration, however, rarely assumes notable proportions. The endocardium may be entirely healthy in appearance, but more commonly it has been observed that the lining membrane is extremely thin, transparent, and of bluish-white color. Streaks or spots of fatty degeneration may be seen in the endocardium or shining through the latter from the underlying muscle fibres. Virchow has called attention to the tendency to endocarditis, and Gilbert has particularly noted the occurrence of stenosis of the mitral valve. Some observers have found hypertrophy of the heart affecting the left ventricle or the entire organ. The cause of this is sometimes difficult to determine. Sometimes, as in the remarkable case of Lavinsky, of a child in whom considerable hypertrophy of the heart existed without valvular disease, it is due to a narrowed or contracted condition of the aorta and blood-vessels. In other cases it is probable that the repeated attacks of palpitation and the constant overaction of the heart lead to hypertrophy; while in still others the coexistence of nephritis offers an explanation of the cardiac condition (Bezançon). It is unlikely that hydræmic plethora plays any part in the development of cardiac hypertrophy.

The aorta has frequently been found abnormal and in particular smallness or contraction (hypoplasia) has been looked upon as an important pathological lesion. This condition has been regarded as of such importance that the term *aorta chlorotica* is sometimes applied. The entire aorta may be affected, although in many cases the abdominal portion is particularly small. The root of the artery may be so reduced in diameter that it scarcely admits the little finger, and frequently the abdominal aorta has been found no larger than the normal femoral artery in a person of equal size and age. Besides the smallness of the artery abnormal elasticity of the walls has been found in some cases. At times this has been so striking that the wall of the artery has been compared to rubber from its extreme elasticity. The intima resembles the endocardium, being of a bluish-white color and exceedingly transparent. It is commonly marked by yellowish elevated portions between which the lining of the artery has the bluish color described. A fine network of light-colored portions standing out in relief often gives the interior of the artery a sieve-like appearance.

Microscopic examination reveals more or less marked evidences of fatty degeneration in the elevated portions of the intima, and at times the same process extends to the muscle fibres of the media as well. Finally, it is a feature of the chlorotic aorta that the intercostal branches are irregular in distribution, coming off at irregular intervals instead of regularly in pairs. The aorta alone may be affected or other arteries may be involved at the same time. The arterial hypoplasia may be associated with cardiac hypoplasia or may be entirely independent of the latter.

A number of authors have alluded to the frequency of thrombosis in the veins. This agrees very well with the analysis of the blood made by Becquerel and Rodier, who found increased quantities of fibrin. In a measure it may also be dependent upon the occurrence of fatty degeneration of the intima of the blood-vessels. Proly calls attention to the fact that thrombosis usually occurs after fatigue, and suggests that waste products may enter the circulation and cause changes in the vessel walls. Thrombi have been found in the peripheral veins, in the cardiac chambers, in the pulmonary veins, and particularly in the sinuses within the cranium. In a remarkable case of Hull's, thrombosis extended rapidly from the small saphenous vein of the left side to the popliteal, femoral, common iliac, and cava, and to the large trunks of the right side. Serious œdema and other secondary lesions, even gangrene, may ensue. Arterial thrombosis has been observed in a few cases especially at the base of the brain.

Changes in the Genital Organs.—The persistence of an infantile state of the uterus and ovaries was first noted by Kiwisch, but was more particularly described and brought into general notice by Rokitansky. This hypoplasia, however, has been found absent in certain cases, and has even been substituted by hypertrophy. Virchow, who regarded the cardiovascular changes as more important, distinguished three groups of cases: the first, chlorosis with hypoplasia of the vascular system without notable change in the sexual apparatus; the second, chlorosis with hypoplasia of the vascular system and excessive development of the sexual apparatus; and the third, chlorosis with hypoplasia of the vascular system, and at the same time failure of development of the sexual organs. Others, however, have found the hypoplasia of the genital organs more regularly than that of the cardiovascular system.

The ovaries have usually been found small and poorly developed, having the appearance on microscopic examination of those of children before the age of puberty. The number of Graafian follicles may be notably deficient. Similar conditions are found in the uterus, and, as in infancy, the body and the fundus of the organ may be found

smaller in size than the cervical portion. On the contrary, instances have been reported, especially by Virchow, in which enlargement even to three times the normal size of the ovaries has occurred, and in which the number of Graafian follicles has seemed actually increased. It is difficult, however, to determine whether cases of the latter description do not represent instances in which secondary changes have taken place. The mammary glands are frequently ill-developed, though, on the other hand, they may be quite normal when the disease makes its appearance. Attention has been called to the fact that girls in whom the development of the mammary glands and of the pubes occurs early, and the menses are not established, are liable to a subsequent occurrence of the disease.

The Blood-Making Organs.—Little is known regarding the condition of the blood-making organs. Neumann found the marrow of the bones red, but as such a change may occur in any anæmia of an extreme degree this change is of little practical significance; moreover, it has not been frequently observed. The spleen is sometimes enlarged, and Fuhrer and Scharlau have particularly described cases in which it was enlarged and its substance was pale. Chvostek noted enlargement in twenty-one of fifty-six cases, and Clement reported thirteen instances with splenic hypertrophy. In other cases no change whatever has been discovered.

The pathological changes found throughout the body are in general those of simple anæmia. The skin and visible mucous membranes are pale or of the more characteristic greenish or yellowish color. The subcutaneous fat may be increased in amount, or, on the other hand, may be absorbed, leaving the body considerably emaciated. Preservation of the adipose tissues is a more characteristic condition, and may affect the internal as well as the external fat deposits. Petechial hemorrhages may be found in the skin or mucous membranes, but are rare. Von Hösslin has in particular called attention to small hemorrhages in the mucosa of the gastrointestinal tract, and has looked upon these as important changes.

The liver, the kidneys, the pancreas, and the epithelial glands of the gastrointestinal tract may show fatty changes as in other forms of anæmic disease. Tessier has recorded a case in which fatty disease of the liver was of such degree that scarce any normal cells were present, and the bile, found in the gall bladder, was of a watery character and devoid of bilirubin. Such changes are in no wise characteristic. Changes in the kidneys have been found in certain cases, and have been looked upon as secondary to the vascular hypoplasia. The important alterations noted were sclerosis of the vessels of the organ, with atrophy of the secreting structures proper, notably the glomer-

uli. Such cases have been recorded by Dieulafoy, Bezançon, and Luzet.

Various alterations of the gastrointestinal tract have been discovered. Luton, Hayem, and others have found ulcers in the mucous membrane of the stomach, but these have been generally, and no doubt properly, regarded as secondary changes, and in no way connected with the causation of the disease. The occurrence of fatty degeneration of the epithelium of the glands of the gastric tubules has already been referred to. Dilatation of the stomach is not unusual, and may in certain cases become extreme. Of late years attention has been called to displacement of the stomach or gastroptosis, and certain investigators have looked upon this as important in an etiological sense. Meinert claims to have found it in sixty consecutive cases. Inflammatory changes in the intestines are occasionally observed. Sometimes there is a moderate enteritis; in other cases ulceration has been described. The Egyptian chlorosis of Griesinger, due to the Ankylostoma duodenale, is in reality more allied to pernicious anæmia than to chlorosis.

Changes in the nervous system have been recorded by some as important, although for the most part these have been regarded as functional rather than organic. Copland thought the disease in some way dependent upon asthenia of the sympathetic. Jolly looked upon the pneumogastric as the probable seat of disease, while others have regarded the abdominal ganglia, the splanchnic nerves, or the spinal cord itself as the parts in which the specific lesion occurs.

Changes in the Blood.—The blood as it flows from a puncture or incision is usually strikingly pale in color and abnormally fluid. In most instances there is little difficulty in obtaining large drops from a minute puncture, so that it seems likely that the quantity of blood is not at all reduced. Indeed, Lloyd Jones expresses the belief that the mass is always increased and Henry coincides in this opinon. These conditions were noted by the older writers who described the alteration of the blood as hydræmia. The specific gravity is generally reduced, the reduction being in direct proportion to the diminution of hæmoglobin (Hammerschlag, Devoto, and others). The actual specific gravity has been found to be as low as 1.020.

The specific or characteristic changes affect the red corpuscles and consist in a reduction in the number of these, and more particularly in reduction of the amount of hæmoglobin. The reduction of the number of corpuscles in chlorosis, although it was spoken of by older writers, was first determined by Duncan. It is a notable fact, however, that the degree of oligocythæmia is comparatively insignificant in this disease. The reduction in hæmoglobin and the general dis-

turbances seem to occur primarily; the reduction in the number of corpuscles secondarily. Very many cases are observed in which the reduction of hæmoglobin and the general evidences of anæmia are marked, and in which, notwithstanding, the number of corpuscles scarcely falls below the normal. It is erroneous, however, to state, as does Graeber, that the reduction of the corpuscles is an anæmic complication, while chlorosis in itself is purely a form of oligochromæmia. Every case of chlorosis which has reached a certain degree of severity shows a more or less marked reduction in the number of corpuscles, and in hospital practice it is very unusual to find cases in which the normal number is preserved.

Reinert collected from literature, including his own cases, 247 instances of chlorosis, in which the number of corpuscles was 4,000,000 or more in 99, and below 4,000,000 in 148. This has been the experience of most authors who have recently written of the disease. The following table shows the number of corpuscles and the proportion of hæmoglobin, determined by Fleischl's apparatus, in a number of cases of chlorosis under my own observation:

	Red Blood Corpuscles.	Hæmoglobin.
1.	2,700,000	30 per cent.
2.	3,775,000	50 "
3.	3,412,500	42 "
4.	3,225,000	34 "
5.	4,337,500	54 "
6.	3,600,000	53 "
7.	2,227,000	22 "
8.	3,320,000	30 "
9.	3,800,000	32 "
10.	4,350,000	58 "
11.	3,400,000	45 "
12.	3,550,000	45 "
13.	3,500,000	35 "
14.	4,825,000	56 "
15.	1,500,000	20 "

In extreme cases, as will be seen in the above table, the number may fall as low as 1,500,000, and has even been recorded at 1,000,000. In my own experience the smallest number of corpuscles per cubic millimetre was 1,500,000. In mild or beginning cases the number of corpuscles may be quite the normal. This seems to indicate an early reduction in hæmoglobin, corpuscles being formed in sufficient number, but not of the normal quality. Certain writers have maintained that this condition—normal number of corpuscles and oligochromæmia—results from beginning restoration of the blood, the corpuscles reaching the normal first, as Otto found in post-hemorrhagic anæmia. This view, however, does not seem to me to be

entirely trustworthy. In cases of chlorosis which are improving it does undoubtedly happen that the corpuscles increase more rapidly than the proportion of hæmoglobin; but, on the other hand, the normal number of corpuscles may persist though the hæmoglobin continues to decrease in amount, and when, therefore, it cannot be said that regeneration is taking place.

The individual red corpuscles may show various changes in their general appearance, in their shape and size. When a drop of blood is examined under the microscope the pallor of the individual corpuscle may be at once a striking feature, and when cover-glass preparations are made and stained it may be noted that the erythrocytes are less intensely stained than normal. Occasionally polychromatophilia, the peculiar alteration of protoplasm as a result of which the red corpuscle tends to receive a mixture of colors instead of a single color, has been observed. Maragliano and Castellino assert that the erythrocytes receive basic stains more readily than normal, and look upon this as an evidence of an abnormal tendency to necrobiosis. The shape of the red corpuscles may be more or less altered. In cases in which the number of the corpuscles is little reduced there is generally but little alteration in the shape of the corpuscles, while in cases in which oligocythæmia is pronounced irregular erythrocytes may be quite frequent, and the extremest grades of poikilocytosis may sometimes be discovered.

Microcytes and macrocytes are usually inconspicuous, but may sometimes be present in large numbers. According to Hayem, the average size of the corpuscles falls from the normal (7.5 μ) to 7, 6.5, or even 6 μ. In very severe cases the number of megalocytes increases greatly and may form fifteen, twenty, or thirty per cent. of the total number. Nucleated red corpuscles have been observed, and are supposed by some to have a favorable prognostic significance. The smaller forms or normoblasts are the more frequent, but the large megaloblasts are occasionally seen. Neudorfer has called attention to the occurrence of blood crises, such as von Noorden has seen in pernicious anæmia. These consist in the appearance in the blood of large numbers of normoblasts, occurring paroxysmally and followed by increase in the number of red corpuscles. While these alterations in the shape, size, and the presence of a nucleus have been found in chlorosis they are rarely conspicuous in cases of moderate severity, and are never marked excepting in the severest forms of the disease.

The amount of hæmoglobin is of great importance and oligochromæmia is certainly the most striking feature of the blood in this disease. Hayem spoke of the disease as a chlorosis of the individual corpuscles. Even in the most advanced cases it is found that the

valeur globulaire, or the relative amount of hæmoglobin contained in each corpuscle compared to the normal amount, is constantly decreased. In moderate cases the quantity of hæmoglobin in the corpuscle compared to the normal is from 0.8 to 0.6; in severe cases it falls to 0.5 or even 0.4. Hayem has introduced the term *richesse* to indicate the number of corpuscles that would be found in the blood, with the quantity of hæmoglobin present, provided each corpuscle contained its normal proportion of coloring matter. This *richesse* falls to 3,000,000, 2,000,000, or even 1,000,000 corpuscles in ordinary or severe cases. The same author has further divided the cases of the disease into separate groups according to the number (N) of corpuscles, the *richesse* (R), and the *valeur globulaire* (G), making four groups or degrees:

First, mild cases in which N = 4,000,000, R = 3,080,000, G = 0.77; Second, moderate cases in which N = 4,000,000, R = 2,700,000, G = 0.65; Third, intense cases in which N = 2,900,000, R = 1,500,000, G = 0.52; Fourth, extreme cases of which he observed one instance in which N = 937,000, R = 796,756, G = 0.85.

These figures may be taken as in a measure illustrating the alterations in the number of corpuscles, and in the proportion of hæmoglobin, though of course they are entirely arbitrary. In a study of sixty cases he found twenty of the second degree, thirty-nine of the third, and one of the last degree.

The blood plaques are always increased in number in chlorosis, according to Hayem, who finds in this an explanation of the nature of the disease, holding that the failure of the transformation of blood plaques into red corpuscles is an essential feature in the pathology of the affection. Their number may be increased to 750,000 per cubic millimetre. Von Limbeck confirms this, but other observers have found the increase less striking.

The white corpuscles are usually about normal in number and in their general appearances. Occasionally the number is slightly in excess of the normal (Sörensen, Leichtenstern, Stifler, Reinert). The differential estimations of the various forms of leucocytes have discovered no notable alteration. Occasionally the eosinophile leucocytes are more abundant than normal, and Hammerschlag has found the so-called *markzellen* or myelocytes.

Neusser has attempted to distinguish cases of lymphatic from myelogenic chlorosis. This attempt, however, has met with little success. The lymphatic cases are characterized by a general lymphatic diathesis, tuberculous history, enlargement of the lymphatic glands, and only a moderate reduction in the hæmoglobin. Occasionally a preponderance of lymphocytes is discovered. The myelogenic

forms are distinguished by the greater intensity of the anæmia, by the occurrence of nucleated red corpuscles, irregularly shaped erythrocytes, and eosinophilous leucocytes in abnormal proportion. The spleen may be enlarged and pains in the bones may be complained of.

Studies of the liquid elements of the blood have discovered no characteristic alterations. Maragliano and Castellino, however, have shown that the plasma of chlorosis exercises a destructive influence on normal red corpuscles, and in this opinion they have been confirmed by Gilbert and others. The older authors (Becquerel and Rodier) found the watery elements of the blood increased in chlorosis, and at the same time an increase of albumin, fibrin, and phosphates; while the corpuscles and chloride of sodium were diminished. The increased amount of water has been confirmed by the more accurate studies of Biernacki; but the amount of albumin is decreased, as is the quantity of potassium. The sodium is increased as in other forms of anæmia. The alkalinity has been found increased by Graeber and Drouin, while Krauss, v. Jaksch, v. Limbeck, and Steindler found it normal or decreased. Becquerel and Rodier found the amount of iron decreased and they have been supported by nearly all authorities. A prominent exception is Biernacki, who has found the actual amount of iron normal or even increased in most cases, and never greatly altered. The important alteration in the corpuscles, according to his observations, is the decreased amount of albumin.

Henocque has devised a method for determining the rapidity with which the oxyhæmoglobin becomes reduced, and holds that the reduction occurs more slowly in chlorosis than in health or in ordinary anæmias. As compared with the normal rate of reduction (indicated by the figure 1) the rate in chlorosis is 0.44. In the secondary anæmias reduction occurs twice as rapidly as in chlorosis.

Symptoms.

The onset of the disease is usually gradual, and it may be weeks or even months before the symptoms become sufficiently pronounced to attract attention. Occurring coincidently with the profound changes which take place in the entire organism at the development of puberty and at the establishment of menstruation the first subjective symptoms of the disease may pass unnoticed. In some cases, however, the onset is rather abrupt, and this is particularly the case when nervous influences have been concerned with the establishment of the disease. Usually the first symptoms are subjective in character, the girl becoming listless, easily fatigued, and therefore disin-

clined to play or exercise. The appetite frequently fails and digestion becomes slow and painful. Palpitation of the heart and a tendency to dyspnœa on slight exertion may be marked symptoms. Frequently irritability, peevishness, or marked hysterical manifestations may be early evidences of the disease. Still other cases are first brought under notice by the cessation of menstruation, which had been regularly established or by irregularity in this function. It is a noteworthy fact that some cases present a history of precocious menstruation beginning at the age of twelve or thirteen.

When the disease is fully developed, the appearance of the girl is quite characteristic. The color of the skin is more or less pale and often presents an ashen or yellowish hue, or in brunettes may be somewhat dusky and grayish. Most characteristic of all is the greenish-yellow color which has given to the disease the popular name of "green sickness" and the technical name chlorosis. The change of color in the skin first begins about the ears or around the alæ of the nose and corners of the mouth. The mucous membranes may be affected from the first, particularly the lips, the conjunctiva, and the mucosa of the hard palate. All the visible mucous membranes may be blanched. The condition of the conjunctiva, however, is unreliable, as slight congestion or vasodilatation frequently causes a pinkish color despite advanced anæmia. Occasionally the skin of the body in various places shows areas of light color due to loss of pigment, and in one case I have seen patches of distinct vitiligo. Other parts, such as the flexures of the joints, and particularly the skin covering the dorsal side of the interphalangeal joints, are sometimes darkly pigmented (Bouchard and Pouzet). Acneiform eruptions are not uncommonly seen upon the face, especially during convalescence. The hair may lose its pigment and become light colored in spots.

In contradistinction to the pallor which is the ordinary appearance of chlorotics there are cases in which the lips and cheeks retain their color despite the advanced deterioration of the blood. The color in such cases may be quite high, and the terms *chlorosis florida* (Wendt) or *chlorosis rubra* are aptly applied. The color in these cases is dependent upon vasomotor dilatation and is sometimes extremely changeable under conditions of emotional disturbance, showing a marked degree of vasomotor instability. "It would seem," says Moriez, "that in the chlorotics the circulatory system is inclined to palpitations at the periphery quite as much as at the centre." In such cases the finger nail drawn over the skin may develop an exquisite *tâche rouge*.

The eyes not rarely present characteristic appearances. The

pallor of the conjunctiva has been referred to. The sclera in marked cases has a steel-blue color, while in other cases the yellow color of the subconjunctival fat may cover over the sclera and occasion an appearance resembling that of jaundice.

The subcutaneous tissue is usually well preserved, and some patients tend to become fat rather than to emaciate. The fat, however, is not invariably present. It is due, according to v. Noorden, to the ingestion and absorption of normal quantities of food in persons who, on account of palpitations, dyspnœa, and the like, are prone to avoid exercise, and on account of the feeling of coldness preserve the heat of the body by excessive clothing and external warmth.

Subcutaneous œdema is not infrequent. Usually it appears about the eyelids and beneath the eyes or surrounding the malleoli, and it is more commonly observed towards evening than after rest in the horizontal position. The light color of the skin and the thinness of the latter in some cases give to the œdema a marked peculiarity. Pitting on pressure is usually present when the serous infiltration is marked, but in the earlier stages it may be absent. Generally the œdema is fugacious, disappearing easily when the patient assumes the horizontal position, but moderate œdema may persist despite change of position. Marked dropsy is rare.

Circulatory Disturbances.—Disturbances of the circulation are always prominent in this disease. Not rarely the patients complain of coldness of the extremities, particularly of the feet, and a general feeling of coldness may be a disturbing symptom. In part this is dependent upon derangement of circulation mainly due to vasomotor constriction in the peripheral parts; in part it is due to the condition of the blood itself. Sometimes the skin presents the phenomenon of goose flesh, or *cutis anserina*, in an exquisite manner.

Palpitation.—Palpitation of the heart is rarely absent. It has always been noted as one of the prominent symptoms by writers treating of chlorosis. Under ordinary circumstances, when the patient is at rest and undisturbed by emotional impressions, the cardiac pulsation is conducted with normal rapidity and force; but in cases in which the most extreme degree of anæmia has become established the action of the heart may be constantly more rapid than normal. The slightest physical exertion or emotional disturbance always, however, tends to increase the frequency of the beat, and violent palpitations are not unusual. Some of the older writers, notably Bouillaud, spoke of irregularity of the action of the heart, and the author named in particular applied the expression *folie du cœur*. This, however, is unusual, and as Hayem has pointed out the rhythm of the heart's action is rarely disturbed in uncomplicated cases.

When cardiac dilatation has supervened a fœtal rhythm may be induced, and cases complicated with nephritis may present well marked *bruit de galop*.

Physical examination of the heart may show that the area of cardiac dulness is of normal extent, or, on the other hand, decreased or increased in size. The increase of size not rarely affects the right side in particular, and there may be marked epigastric pulsation. This enlargement of the cardiac area is doubtless due in most instances to dilatation of the heart. Rarely is there actual hypertrophy. The apex beat is usually strong and little displaced. Auscultation over the heart generally reveals murmurs. The most frequent situation is over the base and pulmonary area, the second and third left interspaces, and the murmur is systolic in time. It is generally blowing and superficial in character, but in rare cases may be quite musical or extremely harsh. It is limited quite sharply to the region covering the root of the pulmonary artery. In addition to this murmur, or without a pulmonary murmur, there may be a localized, soft systolic bruit at the apex. This is unaccompanied by palpable thrill and rarely obscures the first sound of the heart. Next in frequency to these, systolic murmurs may be heard over the tricuspid area or in the aortic interspace. In a study of 38 cases Eichhorst found a murmur audible in the pulmonary area 30 times, in the tricuspid area 28 times, in the mitral 27 times, and in the aortic 13 times. As far as loudness of the murmur was concerned, the pulmonary area led with 21 cases, the mitral was second with 9 cases, and the tricuspid third with 8 cases. Barrs found anæmic murmurs in 115 of 205 cases. The murmur was audible at the base alone in 56 cases, at the apex alone in 13, at both places in 24, and at the base, apex, and back in 22.

Diastolic murmurs are extremely rare and are to be considered accidental. Sahli believes them to be venous intrathoracic sounds, but Eichhorst maintains that they are due to dilatation of the root of the aorta or pulmonary artery and consequent regurgitation. The pathology of the ordinary murmurs is still uncertain, but it is probable that disturbances of the action of the cardiac muscle and of the papillary muscles, together with the condition of the blood, and perhaps increased intracardiac tension, are factors in the causation. Some authors have held that they are due to the currents generated in the auricles by the entrance of blood from the veins under conditions of lowered tension. Sometimes they are doubtless due to relative incompetence of the mitral or tricuspid valves resulting from cardiac dilatation. This is particularly likely when the second pulmonary sound is accentuated. Hayem holds that the systolic murmurs

audible at the apex sometimes result from compression of the edge of the left lung.

Next to the palpitations of the heart venous phenomena are frequent and significant. The veins of the neck may be visibly dilated, and may be seen to pulsate with each cardiac contraction. This pulsation may sometimes be due to tricuspid regurgitation consequent upon dilatation of the right ventricle, but in most instances it is a negative pulsation caused by interference with the outflow of the blood from the jugular veins at each cardiac contraction. Palpation over the jugular veins sometimes discovers a fine thrill or *frémissement cataire*. More commonly, however, this is absent, though a bruit may be heard in the veins. The stethoscope being placed over the root of the jugular vein, between the heads of the sterno-cleido-mastoid muscle, a continuous humming or buzzing sound variously termed venous hum, *bruit de diable*, and *nonnengeräusch* is heard. This may be absolutely continuous and unvarying, or systolic increase of the sound may be audible in consequence of the superaddition of an arterial element from the underlying carotid artery, or of additional systolic disturbances of the current in the vein itself. The murmur is more distinct when the head is turned to the opposite side, and the sound may be more distinct during inspiration. This venous hum is more frequently heard upon the right side than upon the left, but in most cases when present is heard on both sides. In a study of 180 cases of typical chlorosis Richardson has found a venous murmur in about one-half of the cases in which the hæmoglobin was below 50 per cent. More accurately, there was no bruit in 49.4 per cent., a right-sided murmur in 33.3 per cent., a left-sided murmur in 6.1 per cent., and a murmur on both sides in 11.1 per cent. Other observers—and my own experience coincides with this—have found the venous bruit more frequent. Though most marked in the cervical veins it may be audible in the femoral where the saphenous enters it, the subclavian, and even in the facial or other smaller veins.

Arterial pulsations and murmurs are less important. While the patient is at rest the arteries may pulsate but little or not at all. With the onset of palpitation, however, marked arterial pulsation may be noted in the carotid or other superficial arteries. In advanced cases and in febrile chlorosis constant arterial pulsation may occur. Auscultation over the course of the artery may discover various sounds or murmurs. With moderate pressure of the stethoscope a sound resembling the systolic sound of the heart may be audible, while on great pressure this is transformed into a blowing murmur. In most if not all cases, arterial murmurs are dependent upon the pressure exerted from without.

The pulse varies in frequency and in character in the same patient as well as in different patients. It is usually inclined to be sharp and weak, the tension generally seeming to be reduced. Bihler made studies of fifty cases with v. Basch's sphygmomometer and found that the blood pressure was diminished in all cases. Lorrain in his sphygmographic studies of numerous cases found nothing beyond slight acceleration and a tendency to dicrotism.

Prominence of the eyeball may be noted in some cases. Usually it is slight, but at times marked exophthalmos may occur. The amount varies with the state of the circulation, being greater or less in proportion to the greater or less distention of the veins.

Enlargement of the thyroid gland is extremely common. Usually the swelling is only moderate, but it is distinctly visible and palpable. In exceptional cases there may be marked enlargement of the gland and even pulsation and thrill are reported to have occurred.

Vasomotor disturbances have already been alluded to. They are most marked in the case of florid chlorosis, in which they manifest themselves by the tendency to flushing and paling of the surface upon slight exertion or emotional excitement. The feeling of coldness and the pallor to a certain extent are dependent upon vasomotor contraction. There is ordinarily little tendency to sweat, but occasionally excessive perspiration may be noted.

Hemorrhages are not unusual. Some patients exhibit a strong tendency to repeated nose-bleed, and this may contribute much to the progressive deterioration of the blood. Arterial degeneration and the character of the blood are active in these cases, but cardiac weakness may be an auxiliary factor in the occurrence of epistaxis. A more serious but much rarer form of hemorrhage is hæmatemesis. This has been noted at all stages of the disease, and has been seen in certain cases even before the development of the affection had become noticeable. The suspicion of gastric ulcer will always be entertained on the occurrence of hemorrhage from the stomach, and it is probable that many cases in which this symptom has presented itself were really instances of secondary anæmia due to ulcer of the stomach. Uterine hemorrhages have been observed by various writers, and Trousseau in particular has described a form of menorrhagic chlorosis. Excessive bleeding at the menstrual periods and between the periods does occur in a certain proportion of cases, but it is probable that local conditions are generally accountable for these complications.

Respiratory Symptoms.—A tendency to dyspnœa exists in every case in proportion to the degree of anæmia. In the earlier stages exercise and emotional disturbances are necessary to produce dyspnœa; later there may be constant breathlessness. In these cases

the respirations are more rapid than normal and are frequently of a peculiar sighing character, the regular rhythm of the respiratory act being from time to time interrupted by long-drawn inspirations.

Physical examination of the chest usually discovers no striking abnormality, but the vesicular murmur may be weak in correspondence with the general muscular weakness of the patient. A troublesome dry cough may disturb the patient's rest and may cause a suspicion of pulmonary disease. To a large extent this is dependent upon the nervous excitability of the patient rather than upon local conditions. Hoarseness and irritation of the larynx sometimes occur from the dryness of the mucous membrane.

Gastro-Intestinal Symptoms.—Disturbances of the digestive organs of some kind or other rarely fail to occur. The tongue is often somewhat coated, or, on the other hand, may be red and raw in appearance. Fœtor of the breath is at times pronounced. The mouth as a rule is dry and the lips may be quite parched; but increased secretion of saliva and even considerable salivation may occur. The appetite is usually disturbed. The patient often loses the desire for meat and substantial foods and tends to be capricious in the selection of articles of diet. In most cases it is noticeable that the girl prefers acids and sour foods, such as pickles and sharp dressings. In marked cases the patient may consume chalk, plaster from the walls, slate pencils, and various similar substances. Even pronounced geophagia has been observed. It is by no means true, however, that all cases of chlorosis are marked by a tendency to the ingestion of abnormal substances. Von Noorden found in a series of cases that the food taken by the patient voluntarily was quite sufficient in quality and amount to maintain the body weight under normal conditions.

The digestion in chlorosis is usually difficult. The patient complains of heaviness after eating and sometimes of gastralgic pains. The latter may be present only when the stomach is empty, and be relieved by food, or it may develop during the process of digestion, subsiding when the stomach is empty. Usually gastralgia is paroxysmal, occurring only from time to time; in other cases it is continuous but marked by exacerbations. The pain may radiate from the stomach around the side to the back or may travel upwards towards the heart, manifesting itself as a cardialgia. Nausea is not unusual, especially in the morning, and sometimes vomiting occurs.

The physical examination of the stomach and a study of the digestive processes often reveal interesting conditions. Bouchard called attention to the existence of dilatation of the stomach, and Hayem found in the examination of thirty-seven cases evidences of dilatation

in twenty-seven. The severity of the disease seemed to bear a direct relation to the existence and degree of dilatation. It would seem, however, that many of these were instances of gastroptosis rather than of dilatation, both from the manner in which the supposed presence of dilatation was established, and from the fact that recent investigations have shown displacement of the organ to be an extremely common condition. Meinert claims to have found it in sixty consecutive cases. It is certainly not an unusual condition, though, as a rule, it is of moderate degree, representing merely Kussmaul's subvertical position of the stomach. The study of the gastric contents shows that in the majority of cases there is excess of free hydrochloric acid. This has been established at the clinic of Riegel by Osswald, who found excess of HCl in ninety-five per cent. of the cases, and by other investigators. In some cases subacidity does exist, but the older writers improperly assumed that this was the usual condition. The secretion of pepsin and the processes of digestion present no notable abnormalities. The absorption of the food has been shown to be normal by Wallerstein and Lipman-Wulf by comparative studies of the ingesta and of the stools. Eichhorst found that iodine appears in the saliva about twenty minutes after administration of potassium iodide, instead of in ten or fifteen minutes as is the case in health. The difference, however, is slight and the test is scarcely reliable when the differences are not more marked than this.

Of the intestinal disturbances constipation is the most frequent and the most important. Very few cases are found in which it is not present, and not rarely it becomes extreme. Fecal impaction may occur, and secondary diarrhœa from irritation of hard scybalous masses may supervene, the discharges in such cases tending to become mucous or muco-membranous.

The temperature is usually normal or even subnormal. Some of the older writers observed fever in the course of the disease, but it is likely that pernicious anæmia was often mistaken for it. The terms, *Febris seu icterus amantium*, *Febris alba*, etc., indicate the prevalence of this opinion. Mollière, in 1882, however, called renewed attention to the febrile form, and subsequently Leclerc, Trazit, and other French writers contributed to the establishment of the fact that fever may occur in this disease. Usually there is a moderate elevation of the temperature at irregular intervals, but sometimes a continuous moderate febrile movement is seen.

Nervous Symptoms.—A great variety of nervous manifestations occur. Nearly always there is a tendency to irritability or to preoccupation. The patient becomes peevish and often lacrymose. Sometimes positive melancholy marks the disease. The most fre-

quent symptom, however, is headache, which is rarely absent. It may be constant and severe or in other cases is paroxysmal. Neuralgias in various situations may be noted from time to time. Hysterical manifestations such as anæsthesia or hyperæsthesia, mild paresis, or even paralysis and convulsive seizures are occasionally noted. Attention has been called to the association of chorea in chlorotic girls, the chlorosis in these cases acting as a predisposing cause.

Disorders of the special senses are rare. Dimness of vision may occur and complete amaurosis has been observed. The eye grounds are usually pale and optic neuritis and neuroretinitis have been reported by Gowers and others. Mackenzie states that optic neuritis is more common than in pernicious anæmia, while retinal hemorrhages are quite generally recognized to be rare. Yellow spots resembling those seen in albuminuric retinitis have been observed (Knies). Disturbance of hearing is infrequent.

The urine is usually light colored and may be normal in amount, or in some cases, particularly such as manifest marked nervous disturbances, the quantity may be excessive. The solid matters are usually diminished and there is rarely, except in advanced cases, any increased nitrogen elimination. Usually the amounts of urea and uric acid are diminished. The reaction is often alkaline. Certain authors have claimed that the amount of coloring matter or of chromogens is increased, but the investigation of G. Hoppe-Seyler, Garrod, and v. Noorden would indicate that there is no excess of urobilin. Aromatic sulphates have been found in normal or even decreased amount by Rethers and Mörner. Albumin may be present in some cases, but casts are rarely found. A few hyaline casts or cylindroids may be present.

Menstrual Disorders.—The menses may be entirely regular and normal in some cases, but usually disturbances are noted. In the majority of cases they become more and more scanty or complete amenorrhœa is developed. In other cases the color of the menses becomes lighter than normal without further disturbance. The complete suppression may be gradual or may occur suddenly and may precede the development of other symptoms by a considerable interval of time. Menorrhagia has already been referred to as occurring in certain exceptional cases, and hemorrhage between the periods sometimes occurs. Among 65 cases examined by Hayem there was diminution of the menses in 36, complete suppression in 24, and in 4 the periods were normal or somewhat prolonged. In a recent study of 87 cases Townsend found scanty menstruation in 54 per cent., irregularity being present as well in some of these; normal menstruation in 15 per cent., and profuse menses in 11 per

cent.; in 20 per cent. there was amenorrhœa for periods of from two months to a year. Dysmenorrhœa is infrequent, but more commonly leucorrhœa has been noted. Local examination in such cases usually shows erosions or inflammation of the vaginal mucosa or of the cervix. Displacements of the uterus are not infrequent. Sterility has been recorded by some as usual in chlorosis, but it has been frequently found that there was no difficulty of conception, and Hippocrates called attention to the fact that pregnancy is frequently followed by recovery from the disease.

Clinical Varieties.

The severity of the disease varies greatly and varieties may be established according to the severity. Hayem and the French writers generally make the condition of the blood a basis for determining the various grades (see above).

Other varieties, such as the amenorrhœic, dysmenorrhœic, the dyspeptic, or the febrile, may be established according as one group of symptoms or the other becomes more prominent.

Chlorosis tarda, or chlorosis occurring in later life, has received special study. In any case in which the symptoms of the disease are present beyond the twenty-fifth year, the suspicion of recurring chlorosis, or of secondary anæmia resembling chlorosis, must be entertained; but there are undoubted instances in which true chlorosis has occurred in later life. In most cases the patient is from twenty-five to thirty or even thirty-five years of age, and the symptoms are those of the disease as it occurs in younger patients.

Male Chlorosis.—This form is extremely rare. It is characterized by symptoms similar to, but less intense than those seen in girls, and there may be evidences of imperfect development of the cardiovascular system.

Hayem reports an instance where all the boys of a family were affected. One instance only of undoubted male chlorosis has come under my observation.

Course and Duration.

The course of the disease varies extremely. The onset, though usually gradual, may be very abrupt as in the cases recorded by Pidoux, Trousseau, Botkin, and Hayem. The disease is usually marked by decided fluctuations, and spontaneous cures or ameliorations may take place. The course is essentially chronic, though at times the duration is short. It tends in most cases to relapse after recovery or apparent recovery. In the instances in which treatment

has been successful and relapses have occurred within a short time the recovery has generally been only apparent. Recurrences are much less frequent when the treatment is prolonged. Hayem has distinguished two forms, one *temporary* and easily influenced by treatment; the other *constitutional*, resisting treatment and marked by relapses.

It is difficult to assign an exact duration, but the majority of cases recover after six or eight weeks; though subsequently relapses may occur and prolong the disease very greatly.

The prognosis is favorable and the disease is in the immense majority of cases curable. A few instances of a fatal termination in uncomplicated cases have been reported, but the "fatal chlorosis" of the older writers was probably pernicious anæmia in most instances. Intercurrent disease or complications such as thrombosis may determine a fatal issue. The tendency to repeated attacks usually persists until the age of thirty or even beyond. The favorable influence of pregnancy and lactation seen in some cases has already been referred to.

Complications and Sequelæ.

Besides the cardiac disturbances which are symptomatic in chlorosis, there are cardiac disorders which arise as distinct complications. Among these the most important is acute endocarditis affecting the mitral or less frequently the aortic valve. The endocarditis may be simple or may be malignant in character. Hemorrhages occurring in the course of chlorosis have already been referred to. Occasionally they become serious. A more frequent and important complication is thrombosis of the veins. This was first observed by Trousseau but has subsequently been noted by many observers. The femoral vein is frequently involved, giving rise to œdema, phlegmasia, or even to gangrene. Usually but one side—more frequently the left—is affected, although double phlegmasia has been noted. Other peripheral veins may be involved and occasionally the internal veins, notably the pulmonary. The sinuses within the cranium are more commonly involved.

Of the complications affecting the gastrointestinal tract ulcer of the stomach is most important and has been frequently observed. In some cases secondary anæmia due to ulcer of the stomach, may closely resemble true chlorosis, but the latter is undoubtedly often the primary condition. The excess of hydrochloric acid and the anæmic condition probably are important etiological factors.

A few observers have noted nephritis as a complication. In these cases there has usually been an excessive amount of urine with albumin

in considerable quantity and hyaline casts. The general appearance of the patient, the cardiac disturbances, dyspepsia, and dyspnœa, and the examination of the blood serve to indicate the original cause. The secondary manifestations which occur in chronic interstitial nephritis, with which the condition might be mistaken, are absent. Marked œdema is rare and disturbances of vision are absent.

Pulmonary Complications.—Chlorosis may occur in the course of tuberculosis or the latter may follow as a sequel of the former. The etiological relation of tuberculosis and chlorosis has been indicated; but there is also a marked tendency in certain cases, notably those in which hypoplasia of the vascular system exists, to the secondary development of the pulmonary disease. Another relation of tuberculosis and chlorosis is of importance. This is the occurrence of a form of anæmia resembling chlorosis in its general appearances as well as in the characteristics of the blood in patients suffering with pulmonary tuberculosis. It is sometimes extremely difficult to distinguish such cases from true chlorosis when the pulmonary lesion is latent or slight, but the tendency to marked irregular fever and to night sweats, to rapid emaciation, with changes in the urine characteristic of rapid tissue waste, are important indications.

Enlargement of the thyroid gland has already been referred to as symptomatic of certain cases. At times this is quite marked, and it has been held that true exophthalmic goitre may occur in the course of chlorosis in consequence of the debilitated state of the system. It is difficult to determine the truth of this matter, since tachycardia and nervous manifestations are not unusual in simple chlorosis, and the enlargement of the gland may sometimes be quite marked without the suspicion of Graves' disease being entertained. The coincidence, therefore, of enlargement of the gland, tachycardia, and nervous manifestations does not necessarily suffice to establish the diagnosis of intercurrent exophthalmic goitre. Even marked exophthalmos may occur in simple chlorosis.

Sequelæ.—Cardiac, pulmonary, digestive, and nervous disorders may persist after the initial attack of chlorosis has subsided or may serve to prolong the disease.

A conversion of chlorosis into pernicious anæmia has been reported by a number of authorities, and it is not improbable that such a sequel may occur, though it is extremely rare. If the prevailing views of the pathology of pernicious anæmia are correct, we must regard it as probable that additional etiological factors leading to blood destruction supervene in cases in which pernicious anæmia follows chlorosis.

Diagnosis.

The diagnosis of chlorosis must be made by a consideration of the clinical history, together with an examination of the blood. Neither of itself suffices. Laache has maintained that there are cases in which all of the symptoms of chlorosis are present, but in which the examination of the blood reveals no abnormalities. He designates such cases by the title *pseudo-chlorosis*, but other observers have been unable to confirm his views. The occurrence of marked anæmia characterized by yellowish pallor, and cardiac, digestive, and menstrual disturbances in a girl between the ages of fourteen and twenty usually suffices to establish the diagnosis for clinical purposes. When in addition to this there is marked disproportion between the percentage of hæmoglobin and the number of the corpuscles as compared to the normal the diagnosis becomes fairly certain. Nevertheless it must be recognized that certain anæmic conditions of a secondary nature resemble chlorosis very closely in its clinical aspects and even in the condition of the blood. Among these the secondary anæmias of pulmonary tuberculosis, of syphilis, malaria, and cancer, as well as post-hemorrhagic anæmia, must be considered.

Pulmonary tuberculosis at its onset may be characterized by a form of chloroanæmia difficult to distinguish from true chlorosis, and the difficulty of diagnosis is increased by the fact that a tuberculous history is so common in the latter disease. Careful and repeated examinations may establish the pulmonary lesion, and in addition rapid wasting, excess of saline constituents in the urine, and continuous fever and sweats are important elements in the diagnosis. The anæmia may be very marked, but in general is less decided in comparison with the symptoms than is the case in chlorosis. Usually the reduction in hæmoglobin is only moderate and the disproportion between the percentage of coloring matter and the number of red blood corpuscles is less marked than in chlorosis. Finally the cough is more frequently attended with expectoration in tuberculosis and tubercle bacilli may be discovered.

Chloroanæmic conditions have been met with in syphilis, particularly in the secondary stage. This is unusual and the anæmia is rarely as pronounced as in chlorosis. The recognition of other signs of syphilis and the effect of treatment are important.

The anæmia of malaria is less frequently like that of chlorosis, and an examination of the blood usually determines less disproportion in the number of corpuscles and the percentage of hæmoglobin. The parasite is usually readily discovered and the clinical course of the disease is ordinarily easy to recognize.

Post-hemorrhagic anæmia may be recognized by the history of the case, and by the condition of the blood. The latter is prone to be marked by leucocytosis and by the occurrence of nucleated corpuscles, while the oligocythæmia is more decided and the reduction of the hæmoglobin is less marked than in chlorosis. Exceptional cases, however, occur in which a careful study is required to determine the nature of the disease.

Cancer is extremely rare at the age at which chlorosis is common, but must be taken into account when late chlorosis is suspected. In such cases the condition of the blood may distinguish the two affections. Though marked oligochromæmia has been observed in cancer, it is rarely as pronounced as in chlorosis, while the number of corpuscles is more likely to be proportionately reduced. Leucocytosis is more frequent, and according to certain authorities the existence of notable proportions of sugar in the blood is important. In most cases indications of a severe organic disease of the stomach or other organs may be determined.

Pernicious anæmia and chlorosis are usually easily distinguished. The pronounced oligocythæmia of the former is rarely equalled in the most extreme cases of chlorosis. In the severest forms of the latter disease, however, the number of corpuscles has been found below 1,000,000, although I have never seen it below 1,500,000. The percentage of hæmoglobin, however, is nearly always relatively excessive, and the changes in the size and shape of the corpuscles and the occurrence of nucleated erythrocytes are as common in pernicious anæmia as they are rare in chlorosis.

Treatment.

The treatment of chlorosis comprehends attention to the personal hygiene as much as the administration of drugs. The frequent occurrence of the disease in girls placed amid unsanitary surroundings indicates the necessity of careful attention to every detail of the daily life. Rest is of prime importance, and in all cases in which the disease has become well established or in which there is a tendency to long continuance, absolute rest in bed should be the preliminary to treatment. After the condition of the blood has begun to improve, passive exercise and massage should be instituted, and later general exercise in the open air becomes important. Removal of the patients from the crowded cities to the country, or in hospitals a certain number of hours passed in the solarium, always proves beneficial. In some cases removal to a higher altitude has been recommended and seems to be decidedly advantageous. Particularly is this true of

cases marked by depression and sluggishness of the general bodily functions. The diet of the patient must be regulated according to the digestive functions. Milk, eggs, meat, and vegetables should always be given as far as possible. Von Noorden insists upon the necessity of making the first meal or breakfast a substantial one and states that the disinclination to eat heartily in the morning rapidly subsides when the necessity of so doing is insisted upon. In patients who are not confined to bed it is well to order milk or other food to be taken before rising in the morning. A small amount of alcohol in the form of a light wine may be useful, but individual peculiarity and custom will largely determine this matter.

Regarding the medicinal treatment, a most important element is iron. This may be administered in various forms and unquestionably exerts an influence little short of specific in the treatment of the disease.

Regarding the manner in which iron proves beneficial in chlorosis a wide difference of opinion has existed and to a certain extent still exists. The most natural assumption was adopted after the discovery that the quantity of iron is decreased in this disease, viz., that the iron administered is directly absorbed and thus supplies the deficiency in the blood. This assumption, however, cannot be strictly maintained. In the first place there are few individuals, even taking into account the subjects of chlorosis with impaired appetite, who do not receive sufficient iron in the food to supply the necessary amounts for the purpose of maintaining the state of the blood. Further, it was questioned by some observers whether the iron administered was absorbed at all, and Bunge constructed the attractive theory already referred to that the iron administered to chlorotic patients proves efficacious only by entering into combination with the sulphuretted hydrogen developed in excess by intestinal putrefaction and thus permits the ferruginous nucleoalbumins of the food to be absorbed. The disproofs of this theory have been indicated above. It was found, for example, that the administration of sulphide of iron itself proved beneficial in chlorosis; that substances quite as prone to enter into combination with sulphur do not exercise the same influence, while other substances, notably arsenic, and other measures of treatment having no influence upon processes of intestinal putrefaction, do have a beneficial effect. Finally, experimental investigation has shown that there is no evidence at all of intestinal putrefaction in many cases of chlorosis.

Against the view that the iron administered in the form of medicine has merely a local action in the intestines may be cited the studies of Gottlieb and Kunkel, which show that the liver of mice or

dogs to which iron had been given was much richer in iron than the liver of animals receiving no such treatment. The activity of iron is therefore of some other sort, and it seems not unlikely that the view for a long time held by certain therapeutists and recently detailed by von Noorden is correct, viz., that iron acts as a direct stimulant to the hæmatopoietic organs. This view agrees very well with the acknowledged fact that other remedies, notably arsenic, sometimes exercise a beneficial effect, and also with the fact that enormous doses of iron (far in excess of the needs of the system so far as the supply for the hæmoglobin is concerned) are sometimes required.

The differences of opinion regarding the use of iron have also extended to the question of the preparation which is to be given. The view has been largely held that the inorganic preparations are not absorbed, while organic preparations of certain kinds are readily assimilated. This view is certainly unsustained by convincing evidence, and clinical experience allows no doubt at all of the value of inorganic preparations. Stockman and Henry hold from practical experience that the latter are more useful than the organic preparations.

The form in which the drug is most frequently administered in this country is Blaud's pill, composed of equal parts of the dried sulphate of iron and the carbonate of potassium. From three to six pills, containing one and one-half grains of each ingredient, administered after the meals usually suffice, but it may be well to increase the dose to eight or even twelve pills per day. Large doses, however, tend to increase constipation and may cause disturbance of the stomach. It has been held by some that the dose of iron as ordinarily given (three-grain pills) is too small, and certainly relatively excessive doses at times seem necessary. Objection has also been made to the alkali in Blaud's pill, Albutt regarding it as unnecessary and Mackenzie holding that a proportion of two parts of the iron to one of the alkali is more useful than the ordinary formula. As the condition of the blood improves, the remedy may be reduced in quantity, but iron in some form must not be withheld until the examination of the blood shows practically a normal percentage of hæmoglobin.

Instead of Blaud's pills, the pill of the carbonate of iron, reduced iron, or the tincture of the chloride of iron (ten to twenty drops three times daily) may be substituted. The pills are often objected to on account of difficulty in swallowing or because they cause gastralgic pain. In such cases some of the liquid preparations may be used.

Hayem and the French writers generally insist that the proto-

salts of iron are more useful than the higher compounds. In particular they laud the protooxalate of iron, giving from three to six grains per day in divided doses after meals.

When the stomach is particularly irritable certain organic preparations, such as the albuminates of iron or ferratin, may be used, but in general these seem less reliable than the inorganic preparations. Iron may be administered hypodermically when the stomach is intolerant. Of the forms thus employed the pyrophosphate in conjunction with the citrate of sodium or ammonium and dialyzed iron have particularly claimed attention. The preparations must be freshly made, but under the best conditions are irritating and cause so much pain that they cannot be continued. Recently Da Costa has made a renewed effort to find a suitable preparation and reports that the ferrous manganese citrate, known unofficinally as ferri et mangani citras, in twenty-per cent. solution may be injected without causing pain and gives most satisfactory results. The usual dose for an adult is fifteen minims, representing three grains of the salt.

In some cases the administration of iron in the form either of pills or of solutions is disturbing, and hypodermic medication cannot well be undertaken. In such instances the use of chalybeate waters may be necessary, and at times these prove more satisfactory than the ordinary forms of administration, even though the stomach is little disturbed by the latter. The waters of Pyrmont, Schwalbach, Spa, and St. Moritz, containing iron in quantities varying from 0.032 to 0.057 per thousand, have been particularly lauded. The waters of Roncegno and Levico, containing both iron and arsenic, sometimes have a distinct advantage, particularly in cases of long duration and marked by tendency to relapses. Artificial chalybeate waters are less valuable, but occasionally those containing the pyrophosphate may be used with advantage.

Next to iron arsenic is of value. As a rule this remedy is to be used only in conjunction with the specific treatment with iron, but at times arsenic alone is of value. It is particularly to be commended when a regeneration of the blood has begun and convalescence is therefore beginning to be established. Fowler's solution may be given in doses of from three to five or ten drops after meals; or the arseniate of sodium or potassium may be combined in Blaud's pills. The separate administration of the remedies, however, has the advantage that either may be increased or decreased, according to the needs of the case. Arsenic waters, such as those already referred to, and those of Bourboule and Plombières, may be employed with advantage in certain cases.

The discovery that the human blood contains a certain proportion of manganese led at one time to the hope that this remedy would prove useful in the treatment of chlorosis, but this hope has not been realized. Manganese is entirely useless.

Schulz and Strübing have recommended the use of sulphur in cases in which iron could not be tolerated in any form. Schulz was of the opinion that there is a deficiency of sulphur in the albumins of the body in chlorosis and that the remedy owes its usefulness to this fact. Investigation has furnished no proof of this assumption, however, and other observers (Eichhorst) have seen no such beneficial effects from the administration of sulphur. Schulz warns against the use of sulphur when gastrointestinal irritation exists in the case.

Various other remedies have been advocated from time to time, but they have not realized the claims made for them and iron and arsenic still remain practically the only medicinal substances having direct value in this disease. In the administration of these remedies it is necessary, however, to measure their effect by repeated examinations of the blood, and as every general practitioner may testify, the cooperation of the patient and the continued use of the remedy are easily obtained when repeated determinations of the hæmoglobin are made, so that the patient realizes the necessity for continuing the treatment. It is a notorious fact that many patients recover from the subjective symptoms and present an entirely healthy appearance long before the hæmoglobin has reached normal proportions, and the frequent failure of treatment in such cases is ascribable to its premature discontinuance more than to the inefficiency of the remedies given. It should be a cardinal rule, therefore, to administer iron until the percentage of hæmoglobin has reached practically the normal. The number of corpuscles is of less significance, since in the process of blood regeneration the normal number of corpuscles is reestablished before the hæmoglobin has reached the normal percentage.

The view of Sir Andrew Clarke that chlorosis is a disease dependent upon gastrointestinal stasis and absorption of toxic substances has led to the employment of purges and intestinal antiseptics. All observers are agreed that constipation, when it is marked, calls for active treatment. The administration of salines, such as Carlsbad salts, Seidlitz powders, or magnesium sulphate in the morning is probably the best mode of causing evacuation of the intestinal contents. At times salines are badly borne by the stomach and a small dose of cascara sagrada administered at bedtime may prove more useful. Aloes or aloin may be advantageously combined in small doses in the ferruginous pills, particularly in cases in which amenorrhœa

is continued. Purgative treatment, however, to the exclusion of specific medication has not received general indorsement.

Intestinal antiseptics of various kinds have been used with more or less apparent advantage. Forchheimer used various preparations, but found salol and hydronaphthol in doses of five grains in combination with some preparation of iron derived from blood most useful. A study of the reports of those advocating this treatment, however, does not seem to indicate greater rapidity of improvement or more striking results than have been obtained by others employing iron alone.

Hydrotherapic Treatment.—Bathing has been advocated in various forms by most of the writers who have treated of this disease. Cold sea bathing undoubtedly exercises a tonic effect in many persons, and it has been prescribed in chlorosis as an adjunct to change of climate, exercise, and other hygienic regulations; but it may be doubted whether the effect is on the whole beneficial. The studies of Murri and of Marcus are important in indicating the disadvantage of cold bathing, the former having found that cold in general exercises a deleterious influence, while the latter held that cold bathing in particular is injurious and even capable of developing the disease in those predisposed to it. Recently hot baths and sweat baths have been employed and appear to exercise a useful effect. Certainly clinical experience would indicate that external warmth is necessary to promote the comfort of the patients if it is not absolutely a requisite in the treatment.

A most extraordinary and at first sight paradoxical form of treatment was instituted by Dyes of Hanover and subsequently lauded by other investigators. This consists of small venesections, from 1 to 2 gm. of blood per kilogram of body weight being abstracted at intervals of a week or more, the patient being kept in bed for twenty-four to forty-eight hours after the venesection. Under this treatment Wilhelmi has found most striking results in fifty-six cases; while Schubert and Scholz have likewise recorded excellent results. Schücking found depression to follow the treatment in some cases and cautions against the extended use of the method.

Inhalations of oxygen have sometimes been recommended, but are of doubtful value. A temporary effect may occasionally be obtained.

Various symptoms may call for special treatment. In particular the condition of the stomach demands attention. Cases in which the digestive processes are slow, and particularly those in which the analysis of the stomach contents shows deficiency of hydrochloric acid, are benefited by the administration of dilute muriatic acid after the

meals. The addition of a stomachic such as gentian, cinchona, or nux vomica is of advantage. Recently I have used in such cases small doses of bicarbonate of soda, combined with nux vomica, and the clinical results seem to justify the belief that the secretion of hydrochloric acid is stimulated by such treatment and the processes of digestion promoted. In the cases in which excess of hydrochloric acid is determined large doses of alkalies administered after the meals or small doses of sedatives like bromide of potassium may prove beneficial. Vomiting may sometimes require treatment. Minute doses of calomel, and sedatives such as cocaine (gr. $\frac{1}{40}$ to $\frac{1}{20}$), dilute hydrocyanic acid (gtt. 1 to 2), and creosote (gtt. $\frac{1}{4}$ to $\frac{1}{2}$), are the most efficient remedies. The latter in combination with gentle counter-irritation or at times with severe external treatment such as cauterization, are also useful when gastralgia is a marked symptom. The cardiac and menstrual disturbances should as a rule receive treatment. Very often officious medication in these directions proves injurious. Excessive cardiac excitement may be relieved by an ice bag or by external warmth and small doses of sedatives. Probably venesection would prove particularly useful in such cases.

Nervous disturbances and particularly headache are sometimes so urgent that the patient resorts to all forms of sedatives and generally with detrimental results. Antipyrin, acetanilid, and phenacetin may temporarily give relief but in the end prove harmful. Attention to the gastrointestinal condition and to the diet and rest usually relieve unpleasant symptoms of this description. General nervous excitability may be favorably influenced by small doses of bromides, but these as a rule disturb the stomach.

Progressive Pernicious Anæmia.

Synonyms.—Idiopathic anæmia (Addison); Essentielle Anämie, and Akute Puerperalchlorose (Lebert); Essentielle maligne or Essentielle febrile Anämie (Immermann); Anæmatosis (Pepper).

Definition.—Progressive pernicious anæmia is a form of extreme anæmia dependent upon a variety of causes or seemingly causeless in origin which tends to increase in severity to a fatal end. It is characterized by marked reduction in the number of red corpuscles, by a preservation of the relative proportion of hæmoglobin, or even by relative excess of hæmoglobin, and by marked changes in the character of the red corpuscles—macrocytes, microcytes, poikilocytes, and nucleated red corpuscles.

The earlier writers in their descriptions of this disease spoke of it as entirely causeless and without characteristic lesions and naturally

looked upon it as a form of extreme interference with the blood-making function.

Later pathological lesions of various kinds were discovered in cases which had clinically presented the features of progressive pernicious anæmia, and other cases were found in which the blood condition seemed dependent upon various disease processes. Some authors have excluded such cases entirely from the group of pernicious anæmia. Others have divided the latter disease into two groups of cases, which they designate as the truly primary or idiopathic and the secondary or symptomatic forms (Eichhorst, Coupland, and others).

It seems to me, however, ill advised to follow either of these plans. The cases which have been separated as being either of a different form (symptomatic or secondary) or as being not at all of the nature of progressive pernicious anæmia are many of them indistinguishable in their manner of onset, in the condition of the blood, in the clinical course, in the prognosis, and in the morbid changes, with exception of those which seem to be the primary cause. The only difference discoverable is the presence of these latter lesions or conditions which may with more or less likelihood be assigned as the cause of the anæmic condition. This, however, is an insufficient reason for excluding such cases from the group of progressive pernicious anæmia, and we have therefore based our definition of the disease upon the condition of the blood and the other clinical manifestations rather than upon any conception of the pathology of the disease or of its etiology.

History.

The earliest description of cases of pernicious anæmia would perhaps be difficult to find. Industrious investigators of different nationalities have succeeded in finding in the literature of their own countrymen descriptions dating to the beginning of the century and have based upon such their claims of priority. Thus the French have pointed out that Andral had described cases as early as 1821, and that others were recorded by Piorry (1840), Trousseau (1857), and Cazenave (1860). The Germans have referred to the descriptions of severe anæmic cases published by Lebert as early as 1853. The English point to the cases of fatal anæmia recorded by Coombe (1823) and Marshall Hall (1837), but the credit of the first accurate description of this disease unquestionably belongs to Addison, who as early as 1843 had described the disease under the name of idiopathic anæmia in his lectures at Guy's Hospital. The detailed description, however, was not published until the appearance of his work on the

"Constitutional and Local Effects of Disease of the Suprarenal Capsules" published in 1855, in which the clinical features of the form of anæmia under consideration are incidentally described.

American literature had not been without references to, and cases of fatal anæmia published before the time of Addison, and in particular credit is due to Channing, who called attention to certain forms of severe or fatal anæmia in a paper published in 1842 ("Notes on Anhæmia, principally in its Connections with the Puerperal State and with Functional Disease of the Uterus; with Cases"). Not only was the disease recognized by Channing, but a group of New England physicians, including Stevenson, Spear, Jackson, McKean, and Ware, recognized and discussed the same affection before and after the time of Channing's publication.

Other American cases were reported by Bennett (1847), Appleton (1851), and Martin (1852), but none of these observers had given an accurate or comprehensive description of the disease in question, and no general recognition of the existence of cases of fatal anæmia may be said to have existed prior to the time of Addison's publication. Even after that time the disease remained comparatively unknown, and the credit of having brought it to general recognition and of having described some of the more important blood changes belongs to Biermer (1868), who also gave to the disease the name by which it is at present most generally known—progressive pernicious anæmia.

Since Biermer's time important additions have been made by Immermann (1874), Zenker (1874), Eichhorst (1876), Quincke (1876), Müller (1877), in Germany and Switzerland; Lépine (1877) and Ferrand (1876), in France; Pye-Smith (1875), Bramwell (1877), Mackenzie (1878), Coupland (1881), and William Hunter (1888), in England; while of the American writers Pepper (1875), Howard (1876), Osler and Gardner (1877) are the most prominent.

Etiology.

Distribution.—Progressive pernicious anæmia is a disease of wide geographical distribution, and cases have been observed in practically all parts of the world. Among the earlier reported cases a large proportion was found in Switzerland, and it was supposed that special influences prevail in that country. Birch-Hirschfeld agrees with Eichhorst and other observers in Switzerland in believing that certain localities are more or less exempt and cites Munich as an instance; while Immermann was led to suggest an epidemic influence on account of its prevalence in certain localities. This, however, is

probably an exaggeration at least. Certain forms of pernicious anæmia, notably those dependent upon parasitic organisms, are doubtless more common in Switzerland and other localities than elsewhere, but beyond that there seems no greater frequency in these than in other parts of the world. In the collected cases tabulated by Pye-Smith the frequency in various countries was as follows: England 51, Switzerland 49, Germany 14, France 6, United States 2, and Italy 1. The relative excess of cases in Switzerland considering the population is striking in these tables as it was in those of other observers of the same period; but in addition to the explanations just given, it may be said that it is probably not so much the result of any special tendency to the affection in Switzerland as of the fact that observers were more alert in the recognition of the disease in that country than elsewhere.

In recent years the disease has been studied in all sections of Germany, France, England, and America, and as accuracy in diagnosis and a general knowledge of the disease have increased, the number of cases observed has coincidently enlarged.

In America the disease is a very common one, and I have myself seen and studied no less than fifteen during the past three years. Osler has had as many as twenty-eight under his observation and other clinicians have had similarly large experience.

Season.—Pernicious anæmia would seem to occur or begin with equal frequency at different times of the year or in different years, though Eichhorst has alluded to late years as constituting a period poor in pernicious anæmia cases as compared with former ones, in his experience. Cases in which remission of the symptoms has occurred tend to relapse in the spring more frequently than at other seasons. I have myself seen several instances of this.

Age.—Pernicious anæmia occurs from infancy to old age, but is more common after middle life than before that time. Of 103 cases collected by Pye-Smith only 10 were found before the age of 20; 29 occurred between 20 and 30; 26 between 30 and 40; 21 between 40 and 50; and 13 between 50 and 60; only 4 occurred after 60. Griffith has succeeded in collecting 10 cases in which the disease occurred before the age of 12, and Monti and Berggrün record 8 additional cases in early childhood. The youngest recorded cases are that of Demme (3 months) and that of Monti and Berggrün (6½ months).

Usually the disease is met with after the age of forty and it may have its onset in persons beyond seventy.

Sex.—Taking all cases together the female sex is more frequently affected than the male; but if the cases of pernicious anæmia due to pregnancy and lactation are excluded, the remaining cases will be

found to be almost equally divided between the sexes. Bristowe and Osler, however, state that it is slightly more common in the male sex. Of my own cases there were eight male and seven female patients, none of the latter being pregnant or parturient women.

Unhygienic Conditions.—Insufficiency of food and confinement, especially when these are combined with overwork and depressing conditions, unquestionably contribute as causes in certain cases. Quincke particularly called attention to instances developing in persons whose diet consisted largely of potatoes and bad coffee, and Hayem described other cases occurring in persons whose diet was chiefly composed of bread and vegetables, badly prepared. The relation of diet to the disease may be somewhat better understood when the influence of certain gastric disorders upon the development of pernicious anæmia has been discussed, though doubtless the mere insufficiency or improper quality of food may be active without actual gastric disease.

It must not, however, be supposed that pernicious anæmia occurs only among the badly fed and ill-nourished. On the contrary, some of the most striking cases that I have seen were in persons whose surroundings were in every way most healthful.

Nervous Influences.—The condition of the nervous system unquestionably holds a close relation to anæmic affections in general, and in particular would seem to have some influence in the causation of pernicious anæmia. This opinion was repeatedly expressed by the older writers, notably Lépine, Wilks, Coupland, and Eichhorst, and was well illustrated by cases reported by Curtin a number of years since.

Whatever the influence exerted through the nervous system may be and in whatever manner it may bring about the disease, certainly cases are not rarely met with in which some unusually severe mental or nervous shock is followed after a short interval by the manifestations of pernicious anæmia. In other cases the onset of the disease is less immediately attributable to shock, but the occurrence of the affection in a person for a long time subject to depressing emotions and severe mental strain or anxiety gives some justification for the view that it is dependent upon nervous influences. Krüger has recently maintained that irritation of the sympathetic nerves giving rise to disturbed functional activity of the spleen is an important factor in the causation of pernicious anæmia as well as of chlorosis, and other investigators have more or less fully coincided in this view.

The effect upon their children of shock and depressed condition of the nervous system in nursing women is of interest as offering a suggestion of the manner in which shock may be active. In a recent case under my own observation a nursing mother was seized

with melancholia of a pronounced type and her infant soon became markedly anæmic. The change was rapid and progressive until artificial food was supplied, when a gradual return to health ensued. The mother herself was somewhat anæmic but not strikingly so. The child, however, was of a waxen color and, although no examinations of its blood could be made, presented external appearances of an intense anæmia, perhaps it might be said of pernicious anæmia. It is not unlikely that intoxication of the child occurred through its mother's milk, and it seems possible also that similar poisons might act upon the individual in whom they were produced.

After this general consideration of conditions which may be more or less active in causing the affection, it is well to consider certain diseases or states of the system which appear to have an immediate connection with pernicious anæmia. Among the conditions are pregnancy and lactation, gastrointestinal disease, and intestinal parasitism.

Pregnancy and Lactation.—The occurrence of a severe and often fatal anæmia in pregnancy and during the puerperal period has been recognized by obstetric writers for a long time. Among the earliest to call attention particularly to this group of cases was Channing, of Massachusetts, to whom reference has already been made. This observer had seen cases of fatal anæmia occurring in pregnancy and recorded a group of such in 1842. Among these one at least occurred as early as 1832. After Channing, Lauth (1852), Lebert (1853), Chalot (1858), and Gusserow (1871) added to the literature of this form of the disease. Some of these cases occurred in the course of pregnancy uncomplicated by any abnormality; in other cases rapid repetition of pregnancy or the loss of blood or complicating affections played an important part. The majority of cases, however, are apparently causeless, the blood undergoing more or less rapid deterioration without the presence of conditions to which this could properly be ascribed. The severe anæmias of lactation are sometimes more easily explained, large losses of blood during labor, puerperal infection, or other complications being the initial conditions upon which the anæmia seems dependent.

Much dispute has arisen as to the propriety of calling such cases instances of pernicious anæmia, but many at least present the characteristic blood condition, the clinical features, and the general course of the disease so that it is probable that they should be included. It is doubtful, however, whether all of the cases recorded as instances of puerperal anæmia are to be included with cases of genuine pernicious anæmia. The great frequency of recovery in these cases may of course be due to the fact that the causes are often transient, but

on the other hand, awakens the suspicion that many of the cases are not pernicious anæmia at all.

Gastrointestinal Diseases.—In a second group of cases lesions have been found in the gastrointestinal tract and notably in the stomach. Fenwick, who was the first to direct attention to this cause of pernicious anæmia, described instances of atrophy and fatty degeneration of the stomach and interstitial gastritis. Similar or analogous conditions were subsequently described by Habershon, Ponfick, Schumann, Nothnagel, Brabazon, Nolen, Henry and Osler, and others. In these cases it is frequently an open question whether the gastric lesion is the cause of the anæmia or its result. In cases of simple fatty degeneration of the gastric tubules it is quite possible that the condition of the stomach is secondary to that of the blood. On the other hand, in instances in which the morbid change in the stomach consists of a high grade of interstitial gastritis or cirrhosis of the stomach it is unlikely that this condition is dependent upon the anæmia. The same may be said of ulcerations or cancer with which pernicious anæmia has occasionally been associated. Similar conditions affecting the intestines may also be met with and probably often play a causal part. The individual conditions of the stomach and intestines will, however, be described in the section on the morbid anatomy of the affection, and further reference to the rôle of these lesions in the causation of the disease will be made in speaking of the pathogenesis.

Animal Parasites.—For a long time severe anæmia has been recognized as the result of the invasion of the intestine by animal parasites, especially by the Ankylostomum duodenale. The anæmia dependent upon ankylostomiasis was recognized by the older observers, such as Bilharz and Griesinger, but was particularly studied by Wucherer (1872). The last-named author spoke of it under the name of tropical chlorosis. In Egypt it was called Egyptian chlorosis, but it has been more recently recognized as having the same general properties and peculiarities as ordinary pernicious anæmia. Subsequently its immediate relation with the latter disease was well illustrated among the laborers engaged in making the St. Gothard tunnel, and since then observers in all parts of the world have reported cases of this description. There have been comparatively few cases in North America, the only one with which I am familiar being one observed in a recent immigrant at St. Louis by Dr. Blickhahn. Within a few months (1896) Bowen has recorded cases which he observed in the Barbadoes. In some parts of South America, however, ankylostomiasis is exceedingly common. The frequency in certain localities may be seen from the fact that Hirsch was able to report one

hundred and twenty-six cases seen in the Fiji Islands in the course of a year, and Sanwith studied four hundred and two at Cairo.

Another parasite that seems to have an etiological relation with pernicious anæmia is the Bothriocephalus latus. Cases of severe anæmia occurring in connection with the presence of this parasite have been recorded by Botkin, Hoffmann, Reyher, Runeberg, Lichtheim, Schapiro, Dehio, and others. The close relation of this worm to the disease is evidenced by the fact that in not a few of the cases observed discharge of the worm has been followed by relief of the anæmic condition. In the case of this parasite as well as of the ankylostomum, however, it must be admitted that pernicious anæmia does not invariably follow the parasitic invasion, and this fact has been made use of by those who would maintain that the anæmia and parasitism have no other relation than that of coincidence. This coincidence, however, is far too frequent to be regarded as purely accidental, and in view of the instances alluded to in which cure has followed discharge of the parasite a causal relation may be considered as definitely established. Reference will be made in discussing the pathogenesis of the affection to the way in which these parasites are active in the production of the disease.

A few cases are recorded in which other intestinal worms have seemed to bear an etiological relation to pernicious anæmia. Among these Botkin and Hoffmann include Tænia solium, Demme records a case apparently due to the presence of Ascaris lumbricoides, and Eisenlohr one associated with the presence of Tænia saginata, but in these cases the diagnosis of the disease and to a less extent the causal relation of the parasite are open to some doubt.

We must next consider certain conditions which have been supposed to bear an immediate relation to the occurrence of pernicious anæmia, but of the importance of which much doubt exists. These are hemorrhage, certain general diseases, and infection.

Hemorrhage.—Certain writers have asserted that large hemorrhages or repeated small hemorrhages are capable of producing an anæmic condition like that of pernicious anæmia, if not this disease itself. Recent investigations, however, show that the condition of the blood after hemorrhages is quite distinct from that of pernicious anæmia, and is specially marked by the great reduction in the quantity of hæmoglobin. In the case of small and frequently repeated hemorrhages, however, it has been held that a condition of the blood is brought about like that of pernicious anæmia, and in particular it has been claimed that the ankylostomum is active by causing such small and frequently repeated losses of blood. This view of the action of the ankylostomum, however, has not met with general ap-

proval and it may be pointed out that in some of the cases of severe pernicious anæmia occurring in cases of ankylostomiasis a very small number of parasites has been found; whereas in other cases in which very many ankylostoma were present pernicious anæmia did not result. The former of these facts is sufficient to indicate that this parasite does not act by causing hemorrhage.

General Diseases.—Various general diseases have been supposed to bear a relation to pernicious anæmia and in particular malaria, scrofula, tuberculosis, and syphilis have been so regarded. In many of these cases the diagnosis has been more or less doubtful, while the actual relation of the general disease to the anæmic condition has scarcely been established. Extreme anæmia undoubtedly occurs in certain cases of all of these diseases, but only rarely (as in the cases of syphilis recorded by Klein) does the anæmic disease assume the type of pernicious anæmia.

Various conditions causing debilitating discharges (*Säfteverluss*) have been included among the causes of secondary pernicious anæmia by Eichhorst, but both the diagnosis and exact etiology in such cases may be questioned.

Infection.—Finally we may consider the question of the infectiousness of pernicious anæmia. It has already been stated that its unusual prevalence in certain parts of Switzerland led Immermann to regard the disease as possibly infectious. Birch-Hirschfeld, judging from the evidence of pathological studies and in particular from the tissue destruction and the retardation of coagulation, was similarly led to regard the disease as probably infectious in nature. More recently Hunter, Gibson, and others who have looked upon pernicious anæmia as a condition of the blood resulting from intestinal autointoxication, have expressed the belief that various forms of microbic infection of the gastrointestinal tract, or possibly some specific form of such infection, plays an important part in the pathogenesis of this disease. A striking case which points to the probability of this view was one seen by Jürgensen. In this case marked anæmia rapidly disappeared after the administration of purgatives and the discharge of immense numbers of the Bacterium termo. A case of similar significance was reported by Sandoz. In this instance a case of marked and progressive anæmia with prominent gastric symptoms improved rapidly after repeated lavage of the stomach. More recently an analogous case has been reported by Meyer.

Investigators, however, have busied themselves with the study of the blood itself and various micro-organisms have been discovered. Bernheim found small bacilli; Aufrecht a vibrio resembling that of relapsing fever; Klebs, Frankenhäuser, and Petrone certain flagel-

late organisms. It is probable, however, that the latter are merely altered red corpuscles, such as Hayem long since described. These corpuscles are frequently so distorted that they resemble bacilli or monadines, and I have frequently found them presenting the active movements described by Frankenhäuser and the other observers who have found these supposed organisms in the blood of pernicious anæmia. Altogether no progress has resulted from bacteriological studies of the blood, and if the prevailing views of the nature of the disease are correct it is more likely that organisms will be found in the gastrointestinal tract or in other organs rather than in the blood.

Morbid Anatomy.

The surface of the body is generally extremely pallid and not rarely assumes a characteristic lemon-yellow hue. This involves not only the skin but also the conjunctivæ and the other visible mucous membranes. The body is usually not much emaciated, though in certain cases extreme loss of flesh has been observed. As a rule, however, the subcutaneous tissues are preserved and may even increase in bulk so that the patient actually grows stouter as the disease advances. This increase in size is due partly to serous infiltration or dropsy, which is rarely absent about the ankles or beneath the eyes in fatal cases and which may reach the extremest grades of anasarca. Effusions into the serous cavities are not rarely met with. Usually there is but a small quantity of clear liquid in the pleural and pericardial sacs, but in some cases the amount of effusion may be very great. To a large extent, however, the flabbiness and bulkiness of the subcutaneous tissues are due to adipose tissue, and this commonly presents a deep yellow color which suggests icteric staining and which to a large extent is doubtless due to the deposit of hæmatogenous pigment. Lépine has suggested that it is caused by ferrous sulphide. The internal adipose tissues have seemed to me less markedly affected, but throughout the body the fat may have an orange-yellow color. The muscles are usually deep red in color and sometimes have a somewhat yellowish hue. There is generally considerable atrophy, and this is particularly noticeable in contrast with the well-preserved subcutaneous tissues. Sometimes fatty degeneration occurs in the peripheral muscles as also in those of the abdomen and diaphragm. There are certain cases of pernicious anæmia in which the muscles are extremely pale without being otherwise diseased, and cases again in which they present a practically normal appearance.

Ecchymoses may be observed upon the skin, the mucous mem-

branes, or on the serous surfaces. They are more common in the lower extremities than in the upper, and usually present themselves in the form of minute punctate or petechial extravasations into the derma. Occasionally larger suffusions and even extensive extravasations may occur. Similar lesions are seen in the mucous membranes and upon the serous surfaces. While these ecchymoses are by no means rare, they are less common than would appear from many of the descriptions of the morbid anatomy of the disease. As far as my own experience in this matter is concerned they have been present in less than one-half of the cases that have come to autopsy.

Of great importance and frequency are hemorrhages into the retina. These were spoken of by Biermer and more particularly studied by Manz in 1875. Since then they have been noted by all observers. They present themselves in the form of small hemorrhagic extravasations of a rounded or more or less linear shape, disposed in a radiating manner about the optic disc. Frequently the centre of the hemorrhagic area is clear and light colored, this being due in some cases to beginning absorption, in other cases to accumulation of leucocytes, or still again to absence of hemorrhage in that portion. Occasionally retinal hemorrhages are quite extensive.

The Blood.—The greatest interest in the pathology of this disease attaches to the condition of the blood itself.

The quantity of blood in pernicious anæmia has never been satisfactorily determined. In some cases it would seem, however, that the anæmia is not alone a qualitative one, but is also dependent upon a reduction in the mass of the blood. This is particularly true of those cases in which emaciation and desiccation of the tissues are marked and in which the peripheral circulation seems so reduced that blood may be obtained from the finger only after considerable difficulty. Quincke endeavored to determine in two cases the total amount of blood and found it to be respectively 5.0 and 4.34 per cent. of the body weight, in contrast to the normal of about eight per cent. Unfortunately the difficulty in the way of determining this question either clinically or post mortem leaves it a matter of speculation.

As the blood flows from the incision into the finger or other part of the body it usually presents a more or less characteristic appearance. The color is ordinarily light pink or red and the general appearance has been likened to that of water used in washing meat (meat-washings). In certain cases it has been found of a reddish-brown or coffee color or again of an intense brown color, but the light red is the more usual. As a drop of blood rests upon the skin the corpuscular portion soon separates from the clear plasma and the base of the drop may be almost colorless. In most cases the blood

flows freely from a small incision, but occasionally, as was before mentioned, it may be difficult to obtain a single drop.

The specific gravity is usually diminished. Quincke found it as low as 1.0282 in one of his cases and in one of my own it fell to 1.025. This is primarily due to the increased amount of water in the blood, secondarily to decrease of the solid constituents. It is notable, however, that the amount of albumin in the serum is less strikingly reduced than might be expected from the degree of dilution of the blood. The fibrin factors which might seem to be produced from the lack of coagulability observed have been found increased by Marshall and by others in certain cases. Occasionally peptone (?) and albumoses are detected in the blood and xanthin bodies have been observed in considerable proportion.

The greatest interest attaches to the enumeration of the corpuscles and the estimation of the hæmoglobin. Marked reduction in the number of red corpuscles or erythrocytes is perhaps the most significant and characteristic feature of the disease. This reduction or oligocythæmia usually falls to 1,000,000, or 20 per cent. of the normal, and is frequently found to reach 800,000 or 600,000 (16 to 12 per cent.). The greatest reduction recorded in a case which recovered was that found by Quincke, the count being 143,000. The lowest count I have myself observed was 450,000. In studying a case during a prolonged period it is usually found that the number of corpuscles falls rapidly to 1,000,000 and then more slowly; and it may remain stationary for a long time. During periods of improvement the number of corpuscles may rapidly increase and at times may almost reach the normal.

The proportion of hæmoglobin is always greatly reduced but is usually much less diminished than that of the corpuscles. This relative excess of hæmoglobin is a fact of very great importance in diagnosis and was first emphasized by Laache and Hayem. The latter has found the "globular richness" (that is, the relative amount of hæmoglobin contained by each corpuscle as compared to the normal amount contained by each corpuscle) to be as much as 1.7. In other words, each corpuscle on an average contained nearly twice as much hæmoglobin as in normal blood. This excess of hæmoglobin is probably to a large extent due to the existence of many large red corpuscles or megalocytes. To a certain extent, however, it is due also to the occurrence of hæmoglobinæmia.

The study of the individual red corpuscles is most important and we distinguish large giant forms, small dwarf corpuscles, irregular forms, and nucleated corpuscles.

Giant red corpuscles or megalocytes are always a striking feature

in the blood of this disease. They were first carefully studied by Hayem, who found that they may constitute fully one-eighth of all of the corpuscles and may have a mean diameter of from 8.5 to 16 μ. Usually they are large, flabby, and strikingly pale corpuscles without discoverable central depression or concavity and which in the stained preparation show their lack of hæmoglobin by the pallor of the central portions. Their outline may be entirely rounded, but more frequently they are somewhat oblong or elliptical, and Henry, who has particularly directed attention to the latter fact, suggests that this is an evidence of the return of the corpuscle to a lower type, that of the reptilian blood.

Small dwarf corpuscles or microcytes which were first described by Masius and Vanlair (1871) are less distinctive of pernicious anæmia and are less striking. In almost all cases, however, there will be found small red corpuscles, some of them scarcely the size of a normal blood plaque, others nearly the size of the normal red corpuscles.

These may be of the ordinary amber color of the erythrocytes, but, as Eichhorst has pointed out, some of them are of intensely high color and high refractive power, as if they contained a large excess of hæmoglobin. The latter forms in particular have been regarded as significant, but they are not observed in all cases and they have been seen in other forms of anæmia.

Irregular red corpuscles are highly significant. Attention was first directed to them by Quincke, who applied the term poikilocytes; later Ehrlich designated them by the term schistocytes. These irregular red corpuscles are of the most varied shape and appearance. In many cases they differ but little from the normal corpuscle, being drawn out into a fine point at one part of the periphery, somewhat as if there were a ciliated attachment. In other cases the corpuscle assumes a lanceolate form, one end being broad and rounded, the other end tapering to a fine extremity. In still other cases the outline of the corpuscle is undulating and irregular or the circumference is broken and angulated. Star-shaped formations, small broken or fragmented corpuscles and club-shaped or other bizarre forms are often seen. The size of these poikilocytes varies very greatly. Some of them are mere points, others reach very considerable dimensions, being as large as 15 μ or even 20 μ in diameter. The color differs with the size as is the case in the normally shaped corpuscles, the larger ones being usually poor in hæmoglobin, the smaller ones comparatively or apparently rich in coloring matter. This, however, is by no means constantly true; many of the smallest poikilocytes are quite devoid of color while the large forms may be quite dark. As a rule the drawn-out extremities are extremely pale, excepting possibly

at the very end; the rounded parts of the corpuscle are usually the darkest.

Occasionally amœboid movements are discovered in the poikilocytes or in the other form of red corpuscles. This phenomenon was

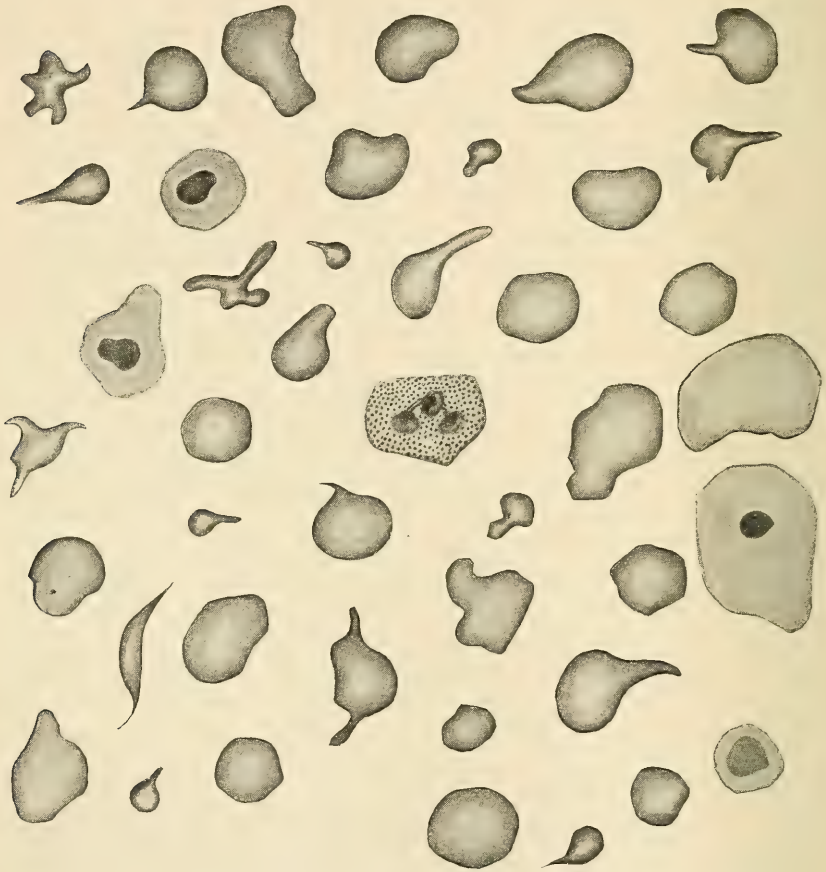

Fig. 38.—Poikilocytes and Nucleated Erythrocytes in Progressive Pernicious Anæmia.

first observed by Friedreich, but was subsequently confirmed by Pilz, Eichhorst, and others. These movements are generally slow and undulating; but Hayem has called attention to another form of movement which affects particularly certain small forms of red corpuscles having a shape not unlike small micrococci or bacilli, the bodies in question being in fact microcytes and poikilocytes of extremely small size. These are sometimes seen to move with considerable rapidity after the fashion of bacteria, and have therefore been appropriately

called pseudo-parasites. It is probable these formations are those which certain observers have mistaken for bacteria and monadines.

Nucleated red corpuscles or erythroblasts are a constant feature of the disease and are of particular significance in indicating the nature and severity of the process. As a rule their number is rather small so that it may be difficult to find more than a few in a cover-slip preparation. In other cases they may be so numerous that scarcely a field can be found in which one or more do not appear. The size of the nucleated red corpuscles varies as does that of the normal forms, and we may distinguish normoblasts, microblasts, and megaloblasts according as the size is normal, small, or large. The term microblast may be applied to the extremely small formations containing nuclei, while the name normoblast is given to those of the average size, which is generally somewhat smaller than that of the non-nucleated red corpuscle. The term megaloblast is given to nucleated erythrocytes of larger size than the normal red cells. In the smaller forms the nuclei usually lie towards one side of the corpuscle, being surrounded by a relatively small amount of protoplasm. In the megaloblasts the nucleus is more centrally located. Preparations treated with nuclear stains show the nuclei of the erythroblasts intensely colored, this being true of the smaller forms in particular. Not rarely karyokinetic figures may be detected and actual division of the nuclei into two or four parts is frequently observed. Granular nuclear degeneration is sometimes seen, especially in the megaloblasts. Certain observers have reported nuclear extrusions as a visible process affecting the normoblasts.

Von Noorden speaks of blood crises, this term being applied to the appearance from time to time of great numbers of normoblasts. The crises last from four to six days and are followed by great increase in the number of corpuscles.

Shadow forms, or *Schatten* (Ponfick), are commonly seen in this disease, though they are rarely abundant. The term is applied to red corpuscles almost entirely devoid of color and visible merely as a pale circle. At times faint granular matter may be observed within them or near the periphery.

Particular attention has been directed to certain peculiarities manifested towards staining reagents in this and other diseases. Normally the red corpuscles when treated after the ordinary method by drying in the air and fixing with heat or chemical substances is monochromatophile, that is, it assumes a single color when stained with mixtures of several stains. In pernicious anæmia it is found that certain of the large megalocytes and sometimes other corpuscles become polychromatophile, so that when the preparation is stained

with hæmatoxylon and eosin, for example, the affected corpuscles present a purple or violaceous color. This has been cited by Ehrlich as an evidence of degeneration and has been held to be of peculiar significance in pernicious anæmia. Neither of these claims can, however, be justified, though the occurrence of corpuscles of this description is quite commonly observed in pernicious anæmia.

The white corpuscles play no prominent or important part in this disease. Frequently in the earlier stages there may be found an actual decrease in their number, but more frequently the number is normal or there is a relative leucocytosis. Towards the end of the disease the number of leucocytes may increase very notably, and the leucocytosis may be sufficient to give rise to the suspicion of leukæmia. Doubtless some of the cases which have been recorded as instances of the transformation of pernicious anæmia into leukæmia have been of this nature. This terminal or preagonal leucocytosis sometimes becomes excessive. The proportion of white corpuscles to red is as one to five or even one to two, the actual number of leucocytes per cubic millimetre being as great as 100,000 or 200,000. Some observers have called attention to the preponderance of large mononuclear forms among the leucocytes of pernicious anæmia. In cases in which there is leucocytosis I have usually found, on the contrary, a great excess of the small lymphocytes, but have also seen large numbers of the mononuclear forms and sometimes typical myelocytes.

The blood plaques vary greatly in number. The difficulty of determining the normal number makes it especially difficult to estimate their relative proportion in pernicious anæmia. Certain authors (Hayem) have held that they are diminished and have made this a ground for asserting that the disease is due to retarded hæmogenesis. Some, however, have found the number increased, and I can confirm the experience of others that there are sometimes surprisingly large numbers as far as one may judge from the groups or clusters observed.

The *heart* presents most important conditions. Biermer had called attention to the fatty degeneration of this organ occurring in pernicious anæmia, but Ponfick in his studies of the fatty heart (1873) was the first to consider it elaborately. Frequently the organ is enlarged; but on the other hand may be much diminished in size. The specific gravity is reduced so that the weight of the organ may be considerably below the normal. The substance is flabby and on section the evidences of fatty degeneration are more or less pronounced. In the case of moderate involvement of the heart the endocardial surface presents a peculiar spotted appearance, due to the presence of lines or rounded areas of yellowish color alternating with

the darker color of the normal endocardium and underlying heart muscle. The term "tabby mottling" has been well applied to this condition. The cross section of the substance of the organ shows a similar contrast of yellowish and dark color from the presence of localized areas of fatty degeneration. When the process is advanced the entire substance is light yellow in color and extremely flabby. At the same time it is friable and may be easily broken with the fingers. The cavities are usually somewhat enlarged, and not rarely extreme dilatation of the chambers occurs shortly before death and is found post mortem. The epicardium presents no characteristic changes, though not rarely the amount of subepicardial fat is quite considerable and may be in excess of the normal.

Within the chambers of the heart may be found blood clots of light color and rather friable structure. Their smallness and light color are decidedly striking in comparison with the conditions usually observed in persons dead of chronic diseases. In other cases the cavities may be almost completely empty, containing no clot at all and only a small amount of pale watery blood. The larger blood-vessels entering the heart rarely contain clots and the entire vascular system is prone to be empty.

The *lungs* present no constant abnormalities. Sometimes small hemorrhages are observed. More frequently the bases of the lungs are œdematous. In the latter case the posterior and basal portions of the lungs are prone to be intensely hyperæmic as compared with the other parts of the organ; but, on the other hand, the œdematous portions may be extremely pallid in color and without any suggestion of hyperæmia. I have rarely seen œdema of the lungs equal that which occurred in two recent cases of pernicious anæmia.

Notable changes are found in the *gastrointestinal tract*. Biermer and the older writers called attention to the fatty condition of the liver, and not a few were disposed to regard this as a most important factor in the etiology of the disease (Perroud). The liver is usually pale, partly in consequence of anæmia and partly in consequence of fatty degeneration. The appearance is usually but little altered, though in some cases the organ is enlarged, and Hanot and Legry have noted simple atrophy. The most important fact in the morbid anatomy of this organ, however, is the abnormal deposit of ferruginous pigment, which was first pointed out by Quincke in 1876 and subsequently studied by Rosenstein, Quincke, Peters, Stahl, Hunter, Griffith and Burr, and others. The iron pigment is demonstrated by treating sections of the tissue with solutions of sulphide of ammonium, which causes a black discoloration due to the formation of sulphide of iron, or by placing the sections in solutions of ferro-

cyanide of potassium for some hours, and subsequently in weak solutions of hydrochloric acid for a similar length of time. In the latter case a discoloration is occasioned by the formation of Prussian blue in the areas containing ferruginous pigment.

These studies show the presence in certain portions of the hepatic substance of large quantities of iron-containing pigment, the quantity in some cases being estimated by Hunter as ten times the normal. Not only is this excess of pigment more or less characteristic of the disease, but additionally the distribution in the hepatic substance seems of prime importance. Hunter and those who have studied the question since his observations find the pigment mainly deposited in the cells of the outer and middle zones of the hepatic lobules. In addition to this, which may be called the essential and characteristic hæmatogenous pigmentation of the hepatic cells, Hunter has more recently described a second form of deposition of iron pigment which occurs in the leucocytes and endothelial cells of the hepatic capillaries and which he holds to be of no significance. In addition to these microchemical tests analyses have been made of the hepatic substance in numbers of cases, and in this manner also (although it must be confessed that this is comparatively unreliable) it has been found that the liver contains excessive quantities of iron. Occasionally hemorrhages have been found in the liver, and Lebert alludes to the occurrence of leucin and tyrosin in excessive quantity in one instance.

The gall bladder is frequently greatly distended with bile, but in other cases no such condition is observed.

Certain pathological conditions of the stomach have been discovered in cases of pernicious anæmia and would seem to bear a close relationship with the disease. Fenwick in 1870 first directed attention to the occurrence of fatty degeneration of the gastric tubules. Subsequently similar conditions of the stomach were reported by Habershon, Ponfick, Schumann, Brabazon, Nothnagel, Nolen, Henry, and Osler. The most frequent condition found in the stomach is that which has been spoken of as fatty degeneration of the tubules. The mucosa may present no striking changes on macroscopic examination, but, on the other hand, may be visibly altered. In the latter instances the walls of the stomach and particularly the mucous membrane may seem to be greatly thinned and at the same time there may be a softer and more friable condition of the mucosa. Microscopically portions treated with osmic acid show a high grade of fatty degeneration of the epithelium of the tubules. In many places a complete destruction of the epithelium may be noted, and the intertubular tissues are found to have undergone a more or less com-

mensurate amount of reactive hyperplasia. Sometimes complete glandular atrophy or destruction is noted, and the lining membrane of the stomach consists of merely flattened epithelium, all semblance of the glandular mucosa having disappeared.

Another class of changes noted in the stomach is characterized by the overgrowth of connective tissue in the mucous membrane and submucosa. The walls of the stomach may become greatly thickened, the mucous membrane hard, and the rugæ either well marked or completely flattened out. Microscopically generalized hyperplasia of the connective-tissue elements and more or less atrophy and degeneration of the glands are the striking features. The submucosa may be converted into a layer of dense, sclerotic connective tissue and its blood-vessels often present marked thickening of their walls. The fibrous-tissue invasion is less pronounced in the mucosa proper, but may extend between the tubules, surrounding them and distorting them to an extreme degree. Cancer of the stomach has been found in certain cases of pernicious anæmia and has seemed to bear a relation closer than that of mere coincidence. Lubarsch has recently described two such cases and one has come under my own notice within a short time.

Somewhat similar affections of the intestines have been described in cases of pernicious anæmia. The relation of intestinal disturbances to anæmia was pointed out as early as 1856 by Wunderlich, and subsequently Grohe, Biermer, and other writers alluded to similar observations. Homolle referred to simple duodenitis in association with pernicious anæmia, while ulcers of the duodenum and stomach were found by Zahn and Litten. Recently in a case under the care of Professor Pepper, mucous colitis seemed to bear an intimate relation to the anæmic affection. Lubarsch reports a case of cancer of the ileum.

Morbid lesions have been described as occurring in the nervous ganglia connected with the stomach and intestines. Thus Jürgensen and Sakaki refer to the occurrence of fatty degeneration and atrophy of the plexuses of Meissner and Auerbach, while Queckett, Wilks, and Brigidi found atrophy, fatty degeneration, and interstitial changes affecting the large sympathetic ganglia of the abdomen, notably the semilunar ganglia.

The pancreas is occasionally found softer than normal and may exhibit considerable parenchymatous or fatty degeneration of the epithelial cells. These changes, however, are neither constant nor of particular significance. Sections stained for iron pigment occasionally exhibit a considerable deposit of such, but not with the regularity observed in the case of the liver.

The *kidneys* usually present marked alteration. As a rule they are enlarged and the capsule may be tensely distended. On section the organs are found to be soft and generally more friable than normal. Their color is intensely pale and the contrast between the cortex and medulla may be exceedingly faint. On the other hand, the medullary pyramids may be congested and in such cases stand out prominently in comparison with the pale cortical substance. The color of the parenchyma is usually a light grayish or yellowish and is ordinarily quite uniform. The capsule of the organ strips easily. Microscopic examination of the sections reveals a high grade of albuminous degeneration and fatty metamorphosis of the renal cells. This is most pronounced in the convoluted tubules, but may affect all parts of the organ. The glomeruli as a rule show no marked alterations, but in some instances hemorrhagic extravasations are observed in this situation. Deposition of iron-containing pigment has been repeatedly observed.

The suprarenal bodies as a rule present no abnormalities, though they may be smaller in size than the normal.

Important alterations have been discovered in the *nervous system* in pernicious anæmia. The entire central nervous system is usually anæmic and the convolutions of the brain may present a shrunken appearance. Not rarely œdema of the membranes and serous exudation may be quite marked. Small capillary hemorrhages are frequently observed in the membranes and in the white matter of the brain or cord. Large hemorrhages rarely occur.

Most important changes have been discovered in the spinal cord. Lichtheim, who first directed attention to this in 1887, reported two cases in which degeneration of the posterior columns and slight changes in the lateral and anterior columns were detected. Subsequently he pointed out that, unlike the changes found in tabes, this degeneration mainly affected the cervical region. Additional cases were observed by Minick, v. Noorden, Eisenlohr, Bowman, Burr, and others. The latter in a study of seven cases has found similar changes to those described by Lichtheim. Areas of degeneration occur in the posterior columns and to a less extent in the lateral tracts. These were almost always symmetrical on the two sides, although occasionally the changes extended farther down upon one side than the other. In the posterior columns the alterations were most marked in the cervical region and often occurred in two portions, one affecting the posterior median, the other the posterior lateral columns. The lesions in the lateral columns were always separated from the posterior roots by an area of normal white matter. The gray matter and the nerve roots are but little affected. Gross deformity

of the cord is never produced. All of the investigators who have studied this subject conclude that the cord changes are such as would be produced by a poison circulating in the blood. There is no evidence that the changes are the result either of hemorrhage or of simple starvation due to anæmia.

Alterations in the Bone Marrow.—In 1875 Pepper and about the same time Fede called attention to the occurrence of changes in the bone marrow in this disease. Subsequently Cohnheim, Scheby-Buch, and others have contributed investigations in the same direction. Briefly, the alteration which occurs in the bone marrow may be said to be a return from the fatty state characteristic of the adult marrow to the embryonal, fœtal, or lymphoid condition. There is in consequence a change from a yellowish or fatty appearance to a more or less red or violaceous color. In some cases the red color is confined to small punctiform or insular areas scattered here and there in the marrow substance. In other cases there is a uniform reddish or violaceous discoloration and the marrow may become extremely soft, almost or quite to diffluence. These changes are characteristic only when seen in the long bones and for the most part may be studied in the tibia. The marrow change may occur rapidly and may at once involve the entire marrow system, or, on the other hand, the appearances may be such as to suggest that the alterations had occurred in an interrupted fashion. Microscopically the important changes are the disappearance of fat cells and an enormous increase of nucleated erythrocytes. In some of the cases I have seen, the fat seemed to have disappeared entirely from the marrow. The preparations made by spreading portions upon cover-glasses, and fixing and staining these according to the methods practised with cover-glass preparations of blood, have presented immense numbers of nucleated corpuscles varying in size from minute forms, scarce a third the size of the normal corpuscle, to the extremest forms of giant erythroblasts. These may contain a single nucleus or one in which more or less fully accomplished nuclear division is taking place. In addition to the nucleated red corpuscles there are non-nucleated forms of all kinds. These are notable especially on account of their great differences in size and shape, and the variation in the amount of hæmoglobin contained. Some are intensely colored, others normal, and still others scarcely visible. Large cells containing erythrocytes are frequently observed. The marrow cells are comparatively inconspicuous but present no abnormal features. These changes in the marrow, however, are neither confined to pernicious anæmia nor are they invariably present in this disease. Neumann long ago pointed out that the marrow changes seen in pernicious

anæmia occur also in other anæmic affections, and that in all probability they are the result rather than the cause of anæmia. Similar changes are seen in advanced cases of secondary anæmia, notably in cancerous cachexia and certain long-continued infections. On the other hand, as was stated, the marrow changes may be absent in certain cases of pernicious anæmia.

Pathogenesis.

The nature of pernicious anæmia has occasioned a very considerable amount of speculation and experimentation. The earlier writers, in consequence of the apparently causeless, progressive, and uncontrollable character of the affection, looked upon it as a vitiation of the blood-making functions and therefore included it in the category of the primary or essential anæmias. In favor of this view they pointed to the occurrence of ill-formed corpuscles, of microcytes and macrocytes, and to the nucleated corpuscles as indications of disturbances of hæmogenesis. After the discovery of the marrow changes this was stated as a still further evidence of the hæmogenic origin of the disease, the marrow changes being looked upon as alterations which might interfere with the proper activity of this structure. Rindfleisch in particular alluded to a case in which practically all of the cells of the marrow were nucleated, and advanced the theory that pernicious anæmia is the result of disturbed hæmogenesis, the latter being brought about by the inability of the nucleated erythrocytes of the marrow to discharge their nuclei and by the consequent arrest of the cycle of development of the red corpuscles.

The discovery by Quincke in 1876 of large quantities of ferruginous pigment in the hepatic cells inaugurated a series of investigations which have had as their result the almost general acceptance of the view that pernicious anæmia is essentially an hæmolytic disease and that disturbance of hæmogenesis plays but an inferior part. This view has been ably developed by William Hunter, to whom the credit of its general acceptance is eminently due. As evidence in favor of the existence of active hæmolysis the occurrence of icterus, of abnormal deposits of hæmatogenous pigment in various organs, the excess of urobilin excreted in the urine, and the occasional occurrence of hæmoglobinæmia may be cited as the most striking. In addition to this it has been found by experimenters, notably by Silbermann, that anæmic conditions resembling pernicious anæmia, may be produced by the injection of hæmolytic poisons into animals, and Hunter and other experimenters have found it possible to produce pigmentation and other results similar to those observed in pernicious anæmia by poisons of the same kind.

Regarding the place of occurrence and the cause of the hæmolysis opinion varies. Hunter, Auld, and others hold to the view that the spleen is the seat of active hæmolysis. On the other hand, evidence is not wanting that the actual hæmolytic processes take place in the liver, and recent studies of the disassociation of hæmoglobin into hæmosiderin and hæmatoidin or one of its congeners would indicate that the hæmolysis of pernicious anæmia must take place in the latter organ. Wherever it may occur the more advanced investigators agree in regarding the disease as essentially a form of toxic hæmolysis and probably dependent upon intestional autointoxication. Certain clinical evidence, such as the cases of Sandoz, Meyer, and Jürgensen, already referred to, and in which pronounced anæmia rapidly subsided after lavage or removal of toxic intestinal contents in other ways, points in this direction. The discovery of excess of indican in the urine (Müller, Senator), the occasional existence of peptonuria, and the discovery of cadaverin and other products of intestinal putrefaction in the urine are more striking indications. These facts, taken in connection with the clinical and pathological discovery of gastro-intestinal disease and pernicious anæmia in association, have led to a quite widespread belief that pernicious anæmia is the result of gastro-intestinal auto-intoxication.

The changes in the bone marrow, in view of the investigations before referred to, must be looked upon as secondary and unessential. They are an evidence of the attempt at compensatory increase of the hæmogenesis and are, therefore, conservative rather than pathogenic processes.

Symptoms.

The general picture of this disease was well portrayed by Addison in his essay on the changes in the suprarenal capsules. "For a long period," he says, "I had from time to time met with a very remarkable form of general anæmia occurring without any discoverable cause whatever, cases in which there had been no previous loss of blood, no exhausting diarrhœa, no chlorosis, no purpura, no renal, splenic, miasmatic, glandular, strumous, or malignant disease." And further on: "It makes its approach in so slow and insidious a manner that the patient can hardly fix a date to the earliest feeling of that languor which is shortly to become so extreme. The countenance gets pale, the whites of the eyes become pearly, the general frame flabby rather than wasted, the pulse perhaps large but remarkably soft and compressible, and occasionally with a slight jerk, especially under the slightest excitement. There is an increasing indisposition to exertion, with an uncomfortable feeling of faintness or

breathlessness on attempting it; the heart is readily made to palpitate; the whole surface of the body presents a blanched, smooth, and waxy appearance; the lips, tongue, and gums seem bloodless, the flabbiness of the solids increases, the appetite fails, extreme languor and faintness supervene; breathlessness and palpitations are produced by the most trifling exertion or emotion; some slight œdema is probably perceived about the ankles; the debility becomes extreme, the patient can no longer rise from bed, the mind occasionally wanders, he falls into a prostrate and half-torpid state, and at length expires; nevertheless, to the very last, and after a sickness of several months' duration, the bulkiness of the general frame and the amount of obesity often present a most striking contrast to the failure and exhaustion observable in every other respect."

This description of Addison of the cases which he designated as idiopathic anæmia was most faithful and in many particulars still serves as an accurate outline of the salient features of the disease.

The onset we find as Addison describes it, slow and insidious, and not rarely there is the difficulty he describes of determining the date of the first manifestations. In other cases, however, the disease begins somewhat abruptly. This is notably the case in some instances of pernicious anæmia occurring during pregnancy or in the puerperal state, and is also noticed in certain cases of pernicious anæmia in which fright or other determining causes have been operative. The onset cannot, however, ever be said to be sudden.

Frequently the first symptom noticed is pallor. This may grow progressively and without interruption or may vary in intensity from time to time. Quite commonly in the beginning there is jaundice which may be a transient condition, but in advanced cases a subicteric hue of the skin is extremely common and is persistent. Eichhorst states that jaundice is rare; in my own experience it was absent in but two of the fifteen cases recently under my observation. The color of the skin in these cases is well described as being lemon yellow and the same hue is observed in the conjunctivæ, while the mucous membrane of the hard and soft palate presents the characteristic color produced by moderate jaundice. In the cases in which jaundice fails to occur, the skin of the patient presents the waxen white color described by Addison.

In the earlier stages of the disease the perspiration may be normal or even excessive, but in advanced cases it is not unusual to find the skin dry and harsh. Some cases are marked by a tendency to flushing and to outbursts of perspiration, which add greatly to the discomfort and weakness of the patient.

The patient usually emaciates very little if at all, and sometimes

the subcutaneous tissues increase in bulk, becoming at the same time remarkably soft and flabby. Occasionally, however, emaciation is noted, and, as in the case of Henry and Osler, may progress rapidly and become extreme. The usual appearance, however, is quite peculiar, and sometimes characteristic. The face is round and fleshy, the limbs and body of the normal size and often conspicuously rounded. The folds about the neck, abdomen, and flexures of the joints may be ample; but when the hand is placed upon any part there is the most striking sense of flabbiness and instability.

Not rarely ecchymoses are seen, especially in the lower extremities. Usually these are small in size, but occasionally they may present themselves as suffusions of considerable dimensions. Similar patechiæ may occur upon the visible mucous surfaces, but are very unusual.

Coincident with the increasing pallor the strength of the patient suffers progressive decrease until at last he is unable to walk or stand. On the other hand, occasional cases are observed in which, despite enormous reduction in the number of corpuscles and in the amount of hæmoglobin, the patient is able to walk or undergo considerable hardships. Usually, however, the disease is characterized by excessive weakness attended with and accentuated by a most extreme degree of languor. This continues progressively and increases until death in fatal cases, or slowly subsides in cases in which a favorable outcome ensues.

Temperature.—The temperature in pernicious anæmia may for a long time be unaffected and there may even be a slightly subnormal curve. As a rule, however, fever is an early symptom, occurring in the form of a mild continuous febrile movement, with marked irregularities; or there may be only occasional elevations from time to time. The degree of the fever rarely exceeds 101° or 102° F., but in occasional instances an elevation to 103° to 104° has been witnessed and may exceptionally persist for quite a length of time. Subsidence of the temperature to a subnormal point is not unusual before death, and in a case published by Müller it fell as low as 24.8° C. (76.6° F.).

The Circulatory System.—In many cases cardiovascular disturbances occur in the early part of the disease and grow in intensity until the end. The circulatory symptoms may thus dominate the clinical picture of the disease. In most cases, however, these symptoms are only of moderate severity, resembling the manifestations on the part of the circulatory system seen in other anæmias, but being somewhat more intense. Palpitation of the heart is usually complained of from the earliest periods of the disease and is particularly marked when the patient makes unusual exertions or suffers

emotional disturbances. In other cases there is a tendency to syncopal attacks and the patient may faint on the least excitement. Pain or distress at the heart is unusual, but in very many cases there is a feeling of heaviness or sinking almost amounting to pain and causing not a little mental distress.

Physical examination of the heart usually discovers some enlargement of the organ, this being due, especially in the later stages of the disease, to dilatation of the chambers of the heart and retraction of the edge of the lungs. The apex beat may be felt as far outwards as the nipple line or even beyond that point as a feeble, fluttering, and ofttimes irregular impulse. Synchronous pulsation in the vessels of the neck is very rarely absent in marked cases. On auscultation over the heart there is usually a more or less decided systolic murmur at the base and in the pulmonic area, and this may extend over the entire præcordia and upwards into the arteries of the neck. The murmur is not heard with the same regularity as in chlorosis, and rarely attains the loudness and superficial character common to that disease. Well-marked murmurs of valvular incompetency may develop with the increasing dilatation of the heart in the later stages. Systolic murmurs are frequently heard in the carotid arteries while a continuous venous hum is discovered in the cervical veins as in chlorosis. The pulse is remarkably quick and soft and not rarely has the characters of the collapsing pulse of aortic regurgitation. In cases in which the cardiac power is comparatively well preserved the capillary pulse of Quincke may be detected. In such cases vascular throbbing and a tendency to flushing of the face and other peripheral parts are not unusual.

Respiratory Symptoms.—Dyspnœa is the most frequent symptom on the part of the respiratory apparatus. In the earlier stages it may be noticeable only when the patient makes exertions or is excited, but in the final period of the disease it becomes a constant and most distressing symptom. Sighing, irregular, or labored respirations are observed from time to time, and in the most advanced stages a form of loud stertorous breathing (anæmic dyspnœa) is often observed. Physical examination detects no abnormalities in the lungs under ordinary conditions, but not rarely in advanced cases œdema of the lung develops, and in addition to increase of dyspnœa and cough with a certain amount of mucous expectoration, physical examination may discover dulness and moist râles at the base. Sometimes these conditions are very marked and may overshadow the other symptoms of the disease. Hydrothorax may be a complication in some cases and may add greatly to the ordinary dyspnœa. A still more serious complication is pneumonia, which is occasionally observed.

Gastrointestinal Symptoms.—The mucous membrane of the mouth is pale and the hard and soft palate may show distinct icteric discoloration. The tongue is usually pale and lightly furred, the covering being light-colored or brownish. In other cases the surface is entirely smooth and red in color. Hemorrhages may occur from the gums and small ulcers may form in various parts of the mouth. The latter symptoms seem on the whole more common in puerperal cases than in ordinary pernicious anæmia. The appetite is generally lost or at least seriously impaired, and not rarely the patient is only with difficulty induced to take sufficient food to maintain life.

Gastric digestion is almost always delayed and more or less disturbed. The patients complain of heaviness or a feeling of pressure or sometimes of actual pain in the epigastrium, these symptoms being more marked after the taking of food. Fermentation with eructation of gas or sour liquid and with flatulent distention of the epigastric region are common and distressing. Sometimes vomiting is a pronounced symptom and in nearly every case it occurs at some period of the disease. In the milder forms the contents of the stomach are ejected at long intervals; in the most serious every attempt to swallow food or drink is followed by vigorous and painful emesis. In one of my cases there was a small amount of blood of altered dark-brownish character in the vomited matters on several occasions and the suspicion of cancer of the stomach was therefore entertained. Actual hæmatemesis may occur but is extremely rare. Examination of the stomach contents usually shows a diminution in the amount of hydrochloric acid or a complete absence of free acid. This was first pointed out by Cahn and von Mering, but it has since been confirmed by numerous observers. It is especially significant and pronounced in the cases in which gastric atrophy or interstitial gastritis is associated with the anæmic condition. The motor activity of the stomach is not rarely deficient, as is evidenced by the abnormal retention of food. Physical examination may detect a certain amount of enlargement of the stomach, and in cases of interstitial gastritis or of gastric carcinoma it may be possible to discover induration or an actual new growth in the epigastrium.

The condition of the bowels is variable. Sometimes there is continuous and extreme constipation, but in the majority of cases there is a tendency from time to time to attacks of diarrhœa, the most usual condition being alternating diarrhœa and constipation. Fermentation and flatulent distention of the intestines may be quite marked. In some cases disease of the colon causing a form of mucous diarrhœa has been noted.

The urine is generally fairly abundant, though it is subject to

great diminution when vomiting or diarrhœa is present. The specific gravity is diminished and the color is variable. Hunter called attention to the fact that excess of coloring matter may occur in the urine of pernicious anæmia, and urged this as one of the evidences of increased hæmolysis. Such an excess of coloring matter, however, is present only in a proportion of cases. The amount of indican has been found increased by Senator and others. Urea is usually increased, though it has been found decreased by some observers; the quantity of uric acid is quite generally acknowledged to be excessive. The saline constituents of the urine are usually diminished. Albuminuria is observed in certain cases and peptone (albumoses) has been found by Laache and others. It is sometimes striking that despite high-grade degeneration of the kidneys but little albumin occurs in the urine. Lactic acid, leucin, and tyrosin have been seen in some cases. Blood corpuscles may be found in some instances and actual hæmaturia has been observed.

The Nervous Symptoms.—Subjective nervous symptoms are not rarely met with in the earlier part or throughout the disease. Among these a feeling of depression or constant fear, a sense of constriction and a tendency to sighing respirations and sleeplessness are notable instances, and are partially explained by the disturbance of the circulation and partly by the condition of the blood itself. Ringing in the ears or buzzing sounds and a tendency to vertigo or to syncope are frequently complained of. Coldness of the feet or hands, dryness of the extremities, or tingling and burning are dependent upon inadequacy of the peripheral circulation. Tremulousness is occasionally seen and is more or less commensurate with the amount of general weakness.

More serious nervous symptoms may occur. In many cases weakness of memory and slowness of intellection are noted, and a hesitancy of speech probably dependent upon intellectual slowness is sometimes striking. As a rule the patient remains entirely unconscious until near the end of the disease, but occasionally delirium or maniacal conditions have been seen in the earlier parts of the affection. While active delirium or mania is quite common just before death, on the other hand a stuporous condition or actual coma may precede the fatal issue by a considerable time. Epileptiform convulsions and hemiplegic seizures or local palsies may occur, the latter being due to cerebral hemorrhages.

Spinal symptoms are not unusual but rarely become pronounced. There may be a little tottering in the gait or marked ataxia may develop. Loss of knee-jerks is common and moderate disturbance of sensation (partial anæsthesia, delayed dermal sensation, mild par-

æsthesia) may occur in the peripheral parts. Bowman has described a case in which the symptoms of spastic paraplegia were observed, and Burr has seen a similar though somewhat questionable instance. Bowman reported another instance in which the symptoms were of the type of disseminated sclerosis.

Ocular Symptoms.—The retinal hemorrhages alluded to in the discussion of the morbid anatomy may occur without accompanying symptoms, or in other cases may give rise to considerable disturbance of vision. Almost complete blindness has been thus occasioned. Ophthalmoscopic examination discovers the hemorrhages more or less numerous in the region surrounding the optic disc. As many as one hundred and twenty have been observed in a single quadrant. They vary in size from mere points to large areas of suffusion and they vary in color from a bright red to a yellowish red as they increase in age. A yellowish or whitish centre is often noted.

Functional disturbances of the other special senses have been reported. Thus sudden deafness and loss of taste or smell or all these combined have been observed.

Course.

The duration of pernicious anæmia is extremely variable. Cases have been observed in which the time that had elapsed from the first notable symptoms until death was only a few weeks. On the other hand, cases running over a period of several or many years are not unusual. The course of the disease when left to itself is generally, as indicated by its name, progressive and pernicious, the deterioration of the blood increasing regularly until the fatal issue. Sometimes, however, there is a tendency to spontaneous improvement from time to time with subsequent relapses until the malady proves fatal. Mackenzie has particularly called attention to the latter form, and has spoken of such cases as instances of relapsing pernicious anæmia. Two instances of this kind have come under my notice, and in one there has been a regular relapse each spring, with improvement during the summer and autumn, for several years.

In cases in which the cause of the disease is removable, as in those due to ankylostoma or bothriocephalus, in puerperal cases, and in some forms of intestinal pernicious anæmia, the termination of the disease may be quite abrupt. Usually when treatment is beneficial the improvement is gradual and is often interrupted by temporary relapses. Intercurrent affections may cause a rapid deterioration, but on the other hand are sometimes overcome with surprising ease.

Complications and Sequelæ.

Most of the complications of the disease have already been noted in the discussion of the symptoms. Those which are likely to prove serious are excessive cardiac weakness from fatty degeneration and dilatation, œdema of the lungs, pneumonia, hemorrhages, excessive diarrhœa of dysenteric character, and nervous complications. Eichhorst and Klebs have seen carcinoma of the stomach develop during the course of pernicious anæmia in several cases. Sarcoma and lymphadenoma have also been described as occurring intercurrently. Reference has already been made to cases in which it was believed that a transition of pernicious anæmia into leukæmia had taken place. Litten described such a case in 1877, the ratio of white to red corpuscles being one to fifteen; and Musser reported one in which the ratio was one to four. It is probable that most of such cases, if not all, are instances of terminal leucocytosis. Little can be said of sequelæ, since the great majority of cases prove fatal. In cases of definite recovery it is likely, however, that degeneration of the nervous system and cardiac or gastric lesions may persist.

Diagnosis.

The diagnosis of pernicious anæmia may sometimes be made by the general appearance of the patient, but finally rests upon the examination of the blood. The peculiar flabby condition of the subcutaneous tissues and the rotundity of the form, nowithstanding the extreme weakness of the patient, are always suggestive though not entirely diagnostic features. When, however, such appearances are met with in a patient in whom causes of secondary anæmia are wanting, the diagnosis becomes quite certain. The occurrence of slight elevations of temperature from time to time or of a continuous moderate febrile movement adds to the clinical picture a further element of suggestiveness.

The condition of the blood, however, furnishes the reliable means of diagnosis. The following points are of special value: The severe grade of oligocythæmia, the relative increase of hæmoglobin, the occurrence of highly irregular corpuscles and of nucleated erythrocytes. The oligocythæmia of pernicious anæmia is extreme. In no other disease does the number of red corpuscles habitually fall to anything near the figure reached in pernicious anæmia. Cases have been recorded of hemorrhage and also of severe internal diseases in which the blood count showed 1,000,000 or even 500,000 corpuscles, but such cases are excessively rare, and I have never met with one in

which the number of corpuscles was below 1,000,000. In all cases in which the number of corpuscles falls below 1,500,000 the suspicion of pernicious anæmia may properly be entertained. The relative excess of hæmoglobin, the excessive *valeur globulaire* of Hayem and Laache, combined with marked oligocythæmia is practically diagnostic, but unfortunately such relative excess of hæmoglobin is not invariable. A number of observers have recorded instances of undoubted pernicious anæmia in which the amount of hæmoglobin was more reduced than the number of the corpuscles; but it is to be noted in these cases that the reduction of hæmoglobin is never much in excess of that of the corpuscles, while in cases of extreme secondary anæmia of any kind a marked disproportion is commonly observed, and in chlorosis the disproportion is extreme. The blood in ten cases I have recently studied gave the following figures:

		Erythrocytes.	Hæmoglobin.
Case	I.	900,000 (18 per cent.)	25 per cent.
"	II.	600,000 (12 ")	15 "
"	III.	1,250,000 (25 ")	30 "
"	IV.	1,200,000 (24 ")	25 "
"	V.	2,000,000 (40 ")	30 "
"	VI.	1,400,000 (28 ")	40 "
"	VII.	1,150,000 (23 ")	40 "
"	VIII.	1,140,000 (22.8 ")	25 "
"	IX.	800,000 (16 ")	35 "
"	X.	900,000 (18 ")	20 "

Regarding the irregular forms of red corpuscle, and the variability in size it may be said that less stress can be laid upon these points than formerly. Poikilocytosis, sometimes of marked degree, is observed in extreme anæmias of all kinds, as are also microcytes and macrocytes. But when these changes are all present in the same case and are marked, the diagnosis of pernicious anæmia may be justified. Nucleated red corpuscless are frequently observed after hemorrhage and in severe anæmias of other kinds, particularly in young persons. In no disease, however, excepting possibly leukæmia, do they occur with the same regularity and frequency as in pernicious anæmia. The large megaloblasts are particularly significant, and when their number predominates over that of the small microcytes the diagnosis of pernicious anæmia is still more certain. The irregular and abnormal manner of staining exhibited by some corpuscles is of no diagnostic value.

Formerly much stress was laid upon the occurrence of retinal hemorrhages, but this has certainly been exaggerated. Retinal hemorrhages occur in a great variety of chronic anæmias of secondary type and are therefore by no means distinctive. Their occur-

rence, however, in a long-continued anæmia without adequate cause would be somewhat significant. Finally, the diagnosis may rest somewhat upon the progress of the case, and the recognition of pernicious anæmia may depend, as did the discovery of the disease, upon the progressive pernicious character of the affection and the uselessness of treatment.

The prominence of certain symptoms in pernicious anæmia, such as the cardiac, the nervous, or the gastric manifestations, may for a time prove misleading and the underlying cause, the anæmia, may be unrecognized. A careful attention to the general condition of the patient and the blood examination will readily eliminate this source of error.

Differential Diagnosis.—Pernicious anæmia must be distinguished from severe secondary anæmias, especially from gastric cancer, and from chlorosis. In the second place it is necessary to distinguish the underlying causes when the existence of the disease has been determined.

The anæmia following hemorrhage is often intense and the face of the patient may present a deathly pallor. Rarely, however, is there the lemon-yellow color so frequently seen in pernicious anæmia. The marked gastric symptoms are absent, as are usually also the elevations of temperature, though the latter have sometimes been observed. The history of the case generally leaves little doubt, pernicious anæmia rarely coming on abruptly. In any case, however, whether the anæmia had an acute onset after a large hemorrhage or a gradual development after repeated small hemorrhages, as from ulcer of the stomach, uterine or rectal hemorrhages, the character of the blood is sufficiently dissimilar to make a differential diagnosis. In acute post-hemorrhagic anæmia the blood rarely shows less than 2,000,000 corpuscles and the hæmoglobin is rarely below forty per cent., death resulting when greater loss of blood has been sustained. In cases of repeated bleeding the blood count may be lower, but the hæmoglobin in these cases is nearly always disproportionately diminished. Blood counts below 1,000,000 are exceedingly rare after hemorrhage and very common in pernicious anæmia. Usually the corpuscles are regular in shape in hemorrhagic anæmia, though their size may vary considerably, and though nucleated corpuscles are observed the microblasts and normoblasts predominate over the megaloblasts. Leucocytosis is more frequent in the earlier periods in hemorrhagic anæmia, while in pernicious anæmia it is usually a terminal symptom.

Gastric cancer may present in its general physiognomy a marked resemblance to pernicious anæmia, and in cases in which the tumor is of such size or location that it cannot readily be felt or discovered

by diagnostic means the diagnosis may remain in doubt. The similarity of the symptoms is dependent upon the prominence of the gastric manifestations in either disease and the long-continued anæmia. Little is learned by the direct examination of the stomach or of its processes, though the discovery of marked motor insufficiency with the development of lactic acid and other products of fermentation, the determination of enlargement of the stomach, and the persistent unvarying absence of hydrochloric acid might furnish some ground for the diagnosis of carcinoma. Further, a tumor in the anterior wall of the stomach might be recognized by the gastrodiaphanoscope, though such a situation would usually permit of discovery by palpation or inflation of the organ. The more important method of diagnosis in these cases is the examination of the blood. The characteristic condition of the blood in carcinoma of the stomach is one which resembles chlorosis more than pernicious anæmia. In some of the most marked cases of anæmia associated with gastric carcinoma that have come under my notice the examination of the blood on an average showed between 2,000,000 and 3,000,000 corpuscles and between thirty and thirty-five per cent. of hæmoglobin. Such a condition of the blood would usually exclude pernicious anæmia, and moreover these counts are most unusual in carcinoma. In the majority of the cases even with decided appearances of anæmia the red corpuscles number above 3,000,000. The corpuscles rarely present the markedly irregular characters seen in pernicious anæmia, though one or the other of the peculiarities noted in that disease may be present. The occurrence of notable quantities of sugar in the blood of carcinoma may prove important but needs further confirmation. Finally it must be remembered that carcinoma of the stomach may actually give rise to the clinical manifestations of pernicious anæmia. This was extremely well marked in a case recently under my own observation, and has been noted by others.

Other forms of secondary anæmia may resemble pernicious anæmia, and I have in particular seen the diagnosis in doubt in certain cases of obscure cardiac disease, cirrhosis of the liver, and interstitial nephritis. Usually, however, the condition of the blood readily determines the diagnosis and careful examination determines the clinical nature of the disease.

Chlorosis and pernicious anæmia are usually distinguished with ease. There are, however, some instances of inveterate chlorosis which eventually resemble pernicious anæmia very closely. This difficulty is most marked in cases of *chlorosis tarda*, or chlorosis in later life. Ordinarily the great reduction in the hæmoglobin with relatively moderate oligocythæmia and the absence of marked aber-

ration in the form and characters of the red corpuscles render the diagnosis comparatively easy. It must be remembered, however, that considerable degrees of oligocythæmia may occur in chlorosis. I have myself found the number of erythrocytes as low as 1,500,000, but in this case there was but fifteen per cent. of hæmoglobin.

The determination of the underlying cause of pernicious anæmia is sometimes easy and sometimes impossible. The gastric origin of certain cases may be plainly indicated by the history and by the symptoms. Thus in one case, which came under my own observation towards the end of the disease, there was a history of fifteen years' treatment for gastric disturbance with growing anæmia, and finally marked accentuation of the gastric troubles with coincident increase of the anæmia until it assumed the characteristics of pernicious anæmia. At the same time the examination of the gastric secretions had given evidence of the entire failure of glandular activity. In another group of cases, such as that reported by Sandoz, distinct evidences of putrefactive fermentation in the stomach or intestinal tract permit the suspicion of a gastrointestinal origin of the disease, and treatment may confirm such suspicion.

The parasitic form of pernicious anæmia may be suspected from the occupation (mining, brickmaking, etc.) of the patient, but is established by examination of the stools. Microscopic examination may show the eggs of bothriocephalus or ankylostoma or segments of the former may be discharged. It is said that retinal hemorrhages and irregularity of the corpuscles both in their shape and in the occurrence of nuclei is more common in the idiopathic forms than in the cases of parasitic anæmia.

The determination of lactation or pregnancy as a cause of pernicious anæmia must of course rest upon the history of the case.

Prognosis.

The prognosis of pernicious anæmia is always extremely grave, though it is not invariably hopeless. The duration of the disease, as has been already remarked, varies from a few weeks to many years, spontaneous recovery occurring in some instances, and in other cases repeated recoveries with relapses rendering the disease quite chronic in its course. Since the introduction of the arsenic treatment a number of cases of definite cure has been recorded, one of Hale White remaining in good health eleven years after his recovery under the use of arsenic. In most cases, however, the apparent recovery is really an incomplete one, and subsequent relapses lead to a final fatal termination. Complete recovery, however, is not rarely observed in

puerperal cases and in parasitic anæmias in which the cause is definitely removable.

Treatment.

The treatment of pernicious anæmia may be considered under three heads: First, the "specific" treatment; second, the treatment directed to alter the general conditions of the circulation; and third, treatment of the intestinal conditions or of underlying affections which influence unfavorably the progress of the case or perhaps act as the immediate causes of the disease.

The "specific" treatment of pernicious anæmia consists in the use of three remedies—iron, arsenic, and bone marrow—and I shall consider them in this order, as it is the order in which they have been brought before the notice of the profession. The value of iron in anæmia is unquestioned. It is particularly valuable in cases of chlorosis and in the ordinary anæmia of debility. Its use has been advocated in pernicious anæmia, and in certain cases good results have been obtained. In most cases, however, iron is of little value, and I am positive that I have seen it contribute to the patient's discomfort and unfavorably influence the progress of the disease, when it was administered during the active stage of pernicious anæmia. In convalescence it is a valuable remedy; and, though the view expressed by some, that iron is practically a necessity at this stage, is probably too radical, there is no doubt that the combination of iron with arsenic or other treatment is most desirable during convalescence in this disease. It may be administered in the form of Blaud's pill, or as an albuminate of iron, or in the form of one of the physiological preparations. The latter, I believe, have no special advantage over some of the inorganic preparations, excepting that they may be more acceptable to the stomach and not so constipating.

Arsenic was introduced by Isnard in 1865, but was more particularly commended by Byrom Bramwell in 1877, to whom the credit of its introduction is due. There is no doubt that in many cases of pernicious anæmia this remedy is little short of a specific. I am inclined to believe that it acts in some way to prevent blood destruction and possibly at the same time to regulate the function of the bone marrow and other blood-making organs. This, however, is largely speculation, and perhaps after all unimportant. The clinical fact remains that this remedy influences favorably the course of the disease.

The administration of arsenic in this disease is a matter of considerable importance. In all cases it should go hand-in-hand with repeated examinations of the blood, and should be regulated by the

response or tolerance of the patient. Sometimes improvement is at once apparent, and only moderate doses are required; in other cases excessive doses, even to the production of toxic symptoms, may fail to influence the course of the disease. Ordinarily Fowler's solution, administered by the mouth in doses of from five to twenty drops three times daily, proves sufficient. If the dose has been increased to twenty drops without noticeable change in the condition of the blood, great care should be exercised in the further increase of the dose. In particular it is to be remembered that gastrointestinal disturbances may be provoked and may cause rapid loss of ground. When this is feared, it is well to administer the remedy hypodermically. Five or ten minims of Fowler's solution, diluted with an equal quantity of water, may readily be administered in this way, and I have never found it specially irritating. Gastrointestinal irritation may occur as in cases in which the remedy is given by the mouth; but this accident is less likely to occur. The results are sometimes quite striking, in contrast with the effects of the administration of like amounts by the mouth.

Bone marrow was introduced as a remedy in the treatment of pernicious anæmia by Fraser, of Edinburgh, in 1894, and has since been used by a number of clinicians, who have reported variable results. The use of bone marrow can scarcely be said to rest upon a scientific basis, and some have objected to it upon the ground that the bone marrow is in no wise an organic secreting tissue, and that in consequence little good may be expected from its administration. It has been held that as the formation of the blood with which the bone marrow is concerned is a process of cell-multiplication rather than a secretion, the administration of extracts could scarcely be expected to give results. On the other hand, it may be said that our knowledge regarding the function of the bone marrow, and particularly its relations to the fluid elements of the blood and to the general metabolism, is so meagre that we are not permitted dogmatically to assert that it is void of action of a chemical sort, and the disproof or proof of the value of this remedy must therefore rest for the present upon clinical experiment rather than upon theory. Some observers have reported cases in which bone marrow seemed a useful remedy, and I have myself observed a case of which the same could be asserted. On the other hand, it has been found useless by some clinicians, and I have seen it fail in one case. It has been claimed by some that the beneficial action occasionally observed is due to the action of iron contained in the bone marrow. Analysis, however, shows that the quantity thus ingested would be wholly insufficient, and the amount of iron taken with other forms of food is greatly in excess of that

taken in this way. Regarding the variability in action in different cases, while it must be admitted that the entire number reported has been insufficient to warrant positive conclusions, I have been inclined to believe that much depends upon the preparation of the marrow. The preparation which has given the best results in my own experience was made by taking equal parts of red marrow and glycerin and mixing these thoroughly in a mortar. A "marrow jam" is thus produced which is palatable and well tolerated by the stomach in quantities of from two to four drachms three or four times daily. A tendency to diarrhœa may in certain patients require reduction in the amount of glycerin contained in the jam. The whole question of the value of bone marrow in pernicious anæmia is undecided.

Next regarding the measures necessary to improve the conditions of the circulation. It is of prime importance in the treatment of a severe anæmic disease, such as the one under consideration, that all of the available corpuscles—none too many at best—be brought into the circulation and rendered useful. For this purpose massage is of great value. It has been pointed out by a number of observers that the corpuscles of the hand held in the air number from five to ten or fifteen per cent. less per cubic millimeter of blood than do those of the toe or other dependent parts. In my own experiments in this direction I have found a uniform excess of from eight to ten per cent. in the blood of the toe, and practically a similar excess of hæmoglobin. Recently J. K. Mitchell demonstrated the advantage of massage to equalize the circulation, and found the number of corpuscles to be thereby quite uniformly increased even in the most pronounced forms of anæmia. It is therefore clear that in the treatment of pernicious anæmia rest in the horizontal position (which will favor the maximum effect for the cardiac action) and massage (which will return to the circulating blood and to usefulness a large proportion of corpuscles) are of considerable importance.

Next to these measures it is of importance to consider the question of quantitative anæmia. Near the end of the disease the patient's condition may be endangered by this reduction in the quantity of blood and the consequent failure of adequate circulation, more than by a deterioration in the quality of the blood, and measures are called for which will increase the blood mass. Injections of large quantities of water or of weak saline solution into the large bowel have the double advantage of stimulating peristalsis and thus improving the general circulation, and perhaps at the same time removing from the system noxious substances, and also the greater advantage of supplying a certain amount of liquid to the empty vessels. In one case of pernicious anæmia which has come under my observation, there was

rapid and unmistakable improvement from the first administration of colonic douches; and while to an extent this improvement was ascribable to improvement in local conditions of the colon, to a large degree it was, I think, owing to absorption of liquid from the bowel.

In certain cases it may be of advantage to substitute for colonic injections hypodermic or intravenous injections. The latter method commends itself particularly in cases in which the circulation has become considerably enfeebled, and absorption of the water is therefore unlikely to occur speedily from the subcutaneous tissues or from the bowel. These methods of increasing the circulation by increasing the quantity of the circulating medium are, I believe, of incalculable advantage in many cases, and failure of arsenic at times is due to the fact that such measures have not been taken to increase the circulation and make the further action of the specific remedy possible.

Brackenridge, von Ziemssen, and others have recently advocated transfusion with defibrinated blood, but there seems little reason to believe, in the light of our present knowledge, that this procedure has any advantage over simple saline injections. The corpuscles introduced with the blood probably rapidly undergo destruction, and it is doubtful whether they are functionally active even for a short time.

The treatment of the underlying affections which perhaps act as the immediate causes of the disease, or which influence unfavorably the progress of a case, comprehends attention to every detail of the patient's physical condition. In particular, however, it is important to consider the question of intestinal antisepsis and other treatment directed to the gastrointestinal tract. The diet should be so selected that the food may readily be digested and that it may undergo as little decomposition as possible. Liquid food, and particularly milk, will prove most useful; and in many cases it is of advantage to have the foods predigested. The quantity at a meal should be small, but food should be given at frequent intervals. Hydrochloric acid and bitters may be used to aid the digestion. Vomiting may be controlled by small doses of bismuth, cocaine, or carbolic acid.

Finally, if our speculations regarding the nature of the disease are correct, and the prime cause is gastrointestinal fermentation, it should be possible to influence favorably the course of the disease by measures directed to the prevention of fermentation in this tract. This has undoubtedly been done in a number of cases. I have already referred to the satisfactory results obtained from colonic lavage in one case; and although this may have been due partly to the absorption of liquid from the bowel, it was doubtless also due, to an extent, to the mere cleansing effect of the injections. Certainly this method of treatment offers sufficient hope of beneficial results to warrant its

more extended introduction. With careful manipulation it is easy to flush the entire colon with water, and probably also a large part of the small intestine; and gastric lavage may be practised with but little inconvenience. This treatment is particularly advisable in cases in which alternating constipation and diarrhœa or excessive vomiting with a fermented condition of the vomited materials give evidence of the gastrointestinal disturbance.

Intestinal antiseptics, such as salol, hydronaphthol, and the like, have been employed, and Gibson in particular has reported good results from this mode of treatment. The failure of intestinal antiseptics to control fermentative processes in other affections, however, makes their use less advisable in pernicious anæmia than theoretical deductions would lead us to expect.

The treatment of pernicious anæmia in association with intestinal parasites is clear and direct. It consists in the administration of remedies such as thymol, santonin, or other anthelmintics, and the subsequent use of tonics, such as arsenic and iron.

Leukæmia.

Synonyms.—Leucocythæmia (Bennett); lymphadénie leucémique (Trousseau).

Definition.

Leukæmia is a disease of hæmatogenesis, characterized by increase in the number of leucocytes in the circulating blood and by characteristic changes in the bone marrow, lymphatic glands, or spleen, or in all of these structures; tending to run a more or less chronic course, and marked by secondary lymphoid infiltrations of various organs.

History.

On October 1st, 1845, Bennett, of Edinburgh, published observations in the *Edinburgh Medical Journal*, under the title of "Two Cases of Disease and Enlargement of the Spleen, in which Death took Place in the Presence of Purulent Matter in the Blood." In the discussion of these cases, he considered the nature of the bodies which he discovered so abundantly in the blood, and decided that they represented white corpuscles, but that no instance had been recorded in which the latter were so numerous. He looked upon his cases as instances of suppuration of the blood, or, as it might be termed, suppurative hæmitis. This opinion was entertained after a careful

investigation of all possible sources of internal suppuration, and he states specifically "that there was no phlebitis or purulent collection to which the appearance within the vessels could be ascribed." Six weeks later Virchow published his first observations in Germany, and, at once realizing the nature of the conditions, applied the term "*weisses Blut*," or leukæmia. He very soon recognized the connection of the latter with disease of the lymphatic or blood-making structures. Active controversy ensued as to the priority in the recognition of the disease, but to Virchow unquestionably belongs the honor of having first actually recognized and described the affection. Bennett relinquished his first view regarding the suppurative nature of the process, and adopted the opinions of Virchow, altering the name of the disease, however, to leucocythæmia.

The credit of having first recognized cases of this disease, however, belongs to much earlier observers. Bichat in 1801, Hodgkin in 1832, Barth and Donné in 1839 (published in 1856), Velpeau, Piorry, Andral, and Rokitansky had all seen cases which with more or less likelihood may be considered to have been leukæmia; and even Morgagni, Galen, and Hippocrates recorded certain suggestive observations of cases of enlargement of the spleen and glands with death from progressive anæmia.

Fuller and Walsh demonstrated the blood changes in the living patient in 1846, and in 1849 the disease was diagnosticated during life by Vogel.

Virchow pointed out that the glands and the spleen may be separately affected, and thus distinguished the lymphatic and splenic or lienal varieties of the disease, in 1853; while Neumann, in 1869, showed that the bone marrow may be involved, and described the medullary or myelogenous variety. Behier (1869) first called attention to the gastrointestinal form of the disease; while Philippart, Nachter, and Kaposi described dermal forms.

After the first observation of the affection by Virchow and Bennett, instances of the disease were recorded with great rapidity, and in his work, published in 1852, Bennett was able to tabulate thirty-seven cases; while in 1860, in his "Lectures on Clinical Medicine," he states that twenty more had come under his notice. Vidal published a monograph in 1856, and since that time numerous comprehensive articles have appeared.

The first case recorded in America was reported by H. J. Bigelow, in Boston, in 1858; and in 1864, Damon, of Boston, issued an interesting monograph. Among the later writings the work of Mosler, of Fleming, of Biesiadecki, of Löwit, and particularly of Ehrlich, have contributed to a more extended knowledge of the affection.

Etiology.

Distribution.—Leukæmia is a disease met with in all parts of the world, though apparently it is more frequent in certain situations. Eichhorst states that he was struck by the frequency of the disease at Königsberg, where numerous cases came under his observation among the Jews coming from Poland to be treated in the hospital of that place, as compared with the occurrence of the disease in Berlin, in Göttingen, and in Jena. During later years, in Zürich, he saw but four cases of this disease among fourteen thousand patients.

Limbeck has collected statistics from the principal hospitals of Europe, and has found the number per 10,000 to vary between quite wide limits. In Würzburg and Barcelona there were 2 cases and 1 case respectively in 22,750 and 59,940 patients; in Brussels and Trieste the proportion was slightly under 1 per 10,000; in Montpellier, Cologne, and Kiel the proportion was about 2 per 10,000; in Munich and Berlin, 2.24 ; in Vienna, Breslau, Innsbruck, and Zürich, about 3.5; in Prague, Leipsic, and Strassburg, between 4 and 5; in Heidelberg, there were 8.87; in Stockholm, 9.18; in Rostock, 9.89. The distribution of the disease in America has not been positively determined, but Osler states that it does not seem to be more frequent in the South than in other parts. Among his 18 cases, 11 occurred in Montreal, 5 in Baltimore, and 2 in Philadelphia. The disease is not uncommon at the present time in the latter city, as I have seen 15 cases during the last four years; and at least 12 have come under my notice within the last year in the hospital service and private practice of myself and colleagues.

Race.—Racial influence does not appear to exert any marked effect. The statement of Eichhorst would seem to indicate a prevalence among the Jews, though the kind of patients seeking hospital aid might have determined this preponderance.

Environment.—The disease is more common among the poor and working classes, but no special influence can be attributed to the social or sanitary surroundings. Cases are frequently seen in those living in luxury and leading a life of ease, as well as in those subjected to squalor or to overwork.

The physical condition of the patient may have been entirely satisfactory before the onset of the disease, or the affection may occur in those whose health has previously suffered.

Age.—Leukæmia occurs at all periods of life, from earliest infancy to advanced years; but the majority of cases occur between the twentieth and the fiftieth year, the maximum for men usually being in the

third decade, and for women in the fourth. In the latter the occurrence of the menopause after forty usually determines the later development of the disease, though leukæmia is by no means infrequent in earlier life.

Sänger records a case of a fœtus, still-born at term, in which the evidences of the disease were discovered. Golitzinsky reported a case in a child one week old, while a number of observers (Orth, Hochsinger and Schiff, Ortner, Stilling, Monti, and Berggrün) have reported cases within the first year. Baginsky stated that from fifteen to twenty per cent. of all the cases occurred in children under ten years of age, and Gerhardt believes it to be as common in childhood as in later life. It has been held that the lymphatic form is more common in children of a few months, while the splenic occurs after the age of one year. In adults the splenomyelogenous form is the more common.

Sex.—Leukæmia is much more common in males than in females. According to Gilbert, it is incomparably more common; and among 200 cases tabulated by Birch-Hirschfeld, 135, or 67.5 per cent., were males, and 65, or 32.5 per cent., were females.

Predisposing Diseases.—Various infectious diseases have been recorded as predisposing or determining the occurrence of leukæmia. Among these, malaria, and especially the irregular chronic forms, has always occupied attention, though it is likely that the occurrence of simple splenic enlargement in this disease counts to some extent for the belief in its etiological importance. In one hundred and fifty cases of leukæmia studied in this connection by Gowers, thirty gave a history of previous malaria; while in the cases under Osler's observation, malaria had been present in one-third.

Syphilis at times seems to play a part, especially the hereditary form of the disease in children. Not rarely lesions have been found post mortem, as in one of the ten cases of acute leukæmia reported by Fraenkel, giving evidence of the previous occurrence of syphilitic infection. Typhoid fever was reported by Immermann as a determining cause in a case of myelogenous leukæmia. Recently attention has been called to influenza by Litten, Fraenkel, and others.

For a long time it has been recognized that disorders of the intestines frequently precede the development of leukæmia, and in particular chronic diarrhœa and dysentery have been recorded. Hinterberger pointed out that many of the cases present stomatitis, lesions of the pharynx, or intestinal ulcers, and suggests that such lesions form the portal of entrance for the infectious specific causes of the disease. Troje believes that in cases of chronic leukæmia in which

early enlargement of the cervical glands occurs, diseased tonsils form the portal of entrance of the infection.

Pregnancy, lactation, and disturbances of menstruation seem to exercise a certain influence in the development of the disease, and Paterson states that in such cases the onset may be abrupt and the course acute. The association of leukæmia with the climacteric has been alluded to before.

Rickets and scrofula occasionally seem to bear an etiological relation to the disease, though many of the cases of supposed leukæmia in association with these affections have doubtless been instances of merely associated leucocytosis.

Heredity is undoubtedly of considerable importance. The most remarkable case is that of Cameron, affecting a woman whose grandmother, mother, and one brother had had symptoms suggesting leukæmia, and who herself had borne two children that died of the disease. During Cameron's observation she passed through three pregnancies, each time giving birth to a non-leukæmic child. Casati reported a case of a girl of ten years suffering with the disease, whose father and grandmother were affected. Biermer observed it in two sisters of three and four and one-half years respectively. Senator saw it in twins of one and one-half years. Eichhorst reports two instances; one in which a child and its cousin were affected, and another in which a child of four had the disease and its brother had died of it at twelve.

The influence of *traumatism*, to which de Chapelle called attention, is sometimes quite striking, though the predisposition to the disease undoubtedly exists in such cases before the traumatism. Ebstein has recently called attention to several cases of a suggestive character, and has treated elaborately of the subject. The reported cases seem to indicate that injuries of the bones or of the spleen are particularly prone to determine the occurrence of leukæmia. Mursick reported a case of acute onset five days after amputation of the thigh, and Credé and Kocher have reported its occurrence after splenectomy.

Cold is supposed to exercise an influence, especially when exposure of the abdomen has occurred. This, however, seems a most unlikely cause.

Pernicious anæmia has been reported in a number of instances as terminating in leukæmia. Striking cases of this character were recorded by Litten and by Musser, but it seems quite likely that some at least of the cases of this character are instances of terminal leucocytosis.

Pseudo-leukæmia and leukæmia are closely allied affections, but

their relation still remains undecided. The lesions of the solid organs are so similar and the occurrence of leucocytosis towards the end of pseudo-leukæmia has been so frequently observed, that certain writers hold to the essential identity of the two affections, looking upon the condition of the blood as a comparatively unessential part of the pathology. Among the Germans, Cohnheim was an advocate of this view; and French writers after Trousseau and Bonfils speak of both affections under the name of adenie, and distinguish two varieties—the leukæmic and the non-leukæmic. Recently this view has gained largely in its adherents, and Troje, in particular, has described pseudo-leukæmia as the forerunner of leukæmia. (See Hodgkin's Disease.)

Infection.—There are many features in leukæmia which make it probable that the disease is essentially infectious in its nature. The character of the lesions and the manner of their metastasis are extremely suspicious, while the clinical course of certain cases, particularly the acute forms, and the occurrence of contagion in at least one recorded instance (Obrastzow) add weight to this assumption. Klebs first suggested the probable infectious nature of the disease, and described certain bodies resembling monadines which he regarded as the probable cause. Subsequently Orth, Osterwald, Roux, and others contributed to this subject. Byrom Bramwell described certain bodies resembling micrococci; Majocchi and Baccini, Kelsch and Vaillard found bacilli in the blood. Pawlowsky discovered bacilli in six cases, the organisms in question being short rods with rounded ends, which could not be cultivated in ordinary media, though he succeeded in obtaining growths upon specially prepared media. Animal experiments, however, were not successful. The bacilli found by Kelsch and Vaillard were pathogenic for mice, and were found in the blood during life, as well as in the tumors post mortem. Staphylococci were discovered in two cases of splenic leukæmia by Bonardi, and very recently bodies resembling coccidia have been found in the lymphatic glands by Mannaberg.

These studies, however, do not serve as yet to establish the infectious origin of the disease; as, on the one hand, negative observations have been recorded by certain observers, and, on the other hand, the occurrence of secondary infections with micrococci and bacilli are extremely common in the course of chronic diseases of all kinds. The attempts which have been made to produce the disease in animals have thus far proved unsuccessful. Mosler injected leukæmic blood into dogs and rabbits without definite results, and Bollinger found that injection of blood from a leukæmic animal into a healthy animal of the same species exercised no specific effect. Gil-

bert, with Cadiot and Roger, has made subcutaneous, intraperitoneal, and intravenous injections of the gland tissues from diseased dogs into healthy dogs; but the results so far have been unconvincing.

Pathological Anatomy.

The essential pathology of leukæmia was first recognized by Virchow. It consists of certain disease processes affecting the lymphatic structures, notably the bone marrow, the spleen, and the lymphatic glands. These processes are of two kinds: First, infiltration with leucocytes, due to the filtering function of the lymphatic structures and the emigration of the leucocytes *in loco*, as Ranvier first pointed out; and secondly, an increase due to actual overgrowth or hyperplasia of lymphadenoid tissue, forming heterologous lymphatic nodes, as Bizzozero, Wertheim, and others have demonstrated. While these changes are primarily found in the lymphatic structures, other organs—as the liver and kidneys, in which lymphatic tissue is normally absent—may be involved; or there may be disease of the lymphoid tissue of the mucous membranes—as in the tonsils, the solitary follicles, and Peyer's patches, in the thymus gland or subcutaneously.

Changes in the Blood-Making Organs.

It is difficult to determine in which part of the hæmopoietic system the pathological changes first make their appearance. Virchow, in his earlier papers, described two forms of the disease—the one characterized by the appearance in the blood of small, round cells, resembling those of lymphatic glands; the other distinguished by the occurrence of large leucocytes with pale nuclei. To the first form the term lymphæmia was applied, and the disease was regarded as essentially a process involving the lymphatic glands. To the second form the term splenæmia or lienal leukæmia was applied, and the place of origin was thought to be the spleen. Subsequently Neumann and others alluded to the changes in the bone marrow discoverable in leukæmia, and the hæmological studies of Cornil, Robin, Ehrlich, and others led to the recognition of the bone marrow as the probable seat of the initial lesions of the disease. Latterly interest has largely turned in this direction, and observers have quite generally looked upon the bone marrow as the essential seat of the disease process.

Bone Marrow.—Changes in the bone marrow were first recognized by Neumann. They occur both in the spongy bones and in the long bones. Ordinarily they are well recognized in the tibia, in the ribs,

sternum, or vertebræ. Two forms of change may be recognized by the macroscopic appearance of the marrow. These were distinguished by Neumann as the pyoid and the lymphoid. In the former of these the marrow presents a more or less yellowish appearance quite different from the light color of normal marrow. The substance of the marrow may be uniformly altered or there may be merely areas scattered here and there in which the appearance is yellow and puriform. The tissue may be firm, but tends more and more to become soft or liquid the further the change has advanced. In the second or lymphoid type of marrow the color is pink or red and the appearances presented are those characteristic of the marrow as found in the fœtus or new-born. Not rarely areas of intense congestion may be seen or small punctate hemorrhages may be visible. In certain cases a mixed character is recognized in the marrow, areas of a yellowish color alternating with other portions having a reddish or violaceous hue. The causes of these differences of appearance are recognized by the microscopic examination. In both forms it is noticed that the fat cells have largely disappeared, and sometimes no trace of fat remains. In the pyoid marrow, as Ponfick pointed out, there is a marked hyperplasia of the colorless marrow cells, while in the lymphoid marrow this peculiarity is less marked, while on the other hand there is more evidence of congestion of the smaller blood-vessels and of the occurrence of masses of nucleated and non-nucleated erythrocytes. Actual hemorrhages may be recognized in certain cases. More careful examination of the pyoid marrow determines that it consists to a large extent of large round hæmoglobin-free cells having large but pale nuclei and abundant fine granules presenting neutrophilic properties. These cells not rarely show active karyokinesis. In the lymphoid marrow the proportion of nucleated red corpuscles is sometimes very large, as in the fœtal marrow and in pernicious anæmia, and a striking proportion of them may show mitotic figures in their nuclei (Troje). Neumann called attention to the fact that the octahedral crystals discovered by Charcot in the blood of leukæmic cases also occur in the marrow of normal individuals after a certain amount of exposure, while in leukæmia, and particularly in cases in which the pyoid condition is noted, the number of such crystals may be decidedly marked.

Cases of leukæmia have been described in which no alteration at all was discovered in the marrow.

Spleen.—Alterations of the spleen are most constant. Usually the splenic changes are associated with medullary changes, and the lieno-medullary form of leukæmia is the most frequent form. The spleen may be greatly enlarged and not rarely extends as far down-

wards as the spine of the ilium and anteriorly as far as the middle line. Almost the entire abdomen may be filled. Sixer records a case in which the weight was sixteen and a half pounds and the size of the organ 37x25 cm. This increase is by no means excessive, and according to Birch-Hirschfeld spleens weighing 5–10 kgm. are not unusual. The leukæmic hypertrophy is essentially variable, the size altering from time to time with alterations in the patient's condition and especially after hemorrhages or diarrhœa. In the earlier stages the organ is hyperæmic and the swelling augments with considerable rapidity. At this time rupture may occur spontaneously or in consequence of traumatism. Later the hyperplastic changes and the infiltration characteristic of the fully developed condition occur. The spleen then becomes harder, and on section the appearance is rather variegated. Hyperæmia of the pulp may cause a reddish or dark-colored appearance of the portions surrounding the blood-vessels, while the adjacent elements are of lighter color. The Malpighian bodies are frequently the special seat of change, becoming of considerable size and light in color. In advanced cases the fixed connective tissue of the trabeculæ tends to undergo thickening and the hardness of the organ may be largely dependent upon diffuse fibrosis. Hyperplastic thickening of the capsule is not uncommon, and inflammatory adhesions may attach the organ firmly to surrounding structures.

The pressure of the excessive infiltration leads to small areas of fatty degeneration or necrosis, and light-colored anæmic infarcts are not uncommon. Hemorrhagic infarcts are less frequently observed. Virchow refers to true abscess of the spleen, and marked pigmentation has been noted in cases following chronic malaria.

Microscopically the essential change consists in the infiltration with and proliferation of lymphoid cells. Usually the cells are small in size, but in places they may be of notable proportions and resemble somewhat the cells of the marrow. Cells enclosing red corpuscles are more or less abundant, and nucleated red corpuscles have been observed; sometimes the latter show karyokinetic changes. Charcot crystals are not unusual and have been demonstrated in several instances in the splenic pulp withdrawn through aspirating needles during life.

Chemical examinations of the splenic substance have varied considerably in their results. Salkowski and Stern found considerable quantities of a substance allied to peptone, with xanthin and tyrosin; while Bockedahl and Landwehr found peptone, lactic acid, succinic acid, xanthin, and leucin, but no tyrosin or hypoxanthin. Stadthagen found xanthin and hypoxanthin with traces of adenin and guanin. None of these observers detected uric acid.

Lymphatic Glands.—Changes in the lymphatic glands may be among the earliest visible symptoms. The glands increase in size, forming large chains or groups. Those of the cervical region are most frequently involved, but the axillary, inguinal, thoracic, and abdominal lymphatic nodes are frequently affected. As a rule the enlargement begins in a single gland or in a small group and spreads until a considerable mass is formed. Usually the individual glands in such masses are more or less intimately connected and fused together, though the normal outlines and limits of each still remain visible. On section the substance is found to be white or pink and rather firm in texture. A certain amount of necrosis may occur within, and spots of yellow color due to fatty degeneration are not unusual. Suppurative softening, however, rarely occurs. Microscopically the changes found consist in proliferation of the cells and also of the vascular channels and of the connective tissue, together with deposition of cells from the blood. Usually the cellular change is in excess of that involving the connective tissue, and the gland in consequence is more or less soft. In certain cases, on the contrary, the glands are of excessive hardness, due to the connective-tissue hyperplasia. The processes may be confined within the capsule of the glands but sometimes extend beyond the latter, and proliferation takes place in the surrounding structures. The individual cells are small round bodies having rather distinct nuclei; though sometimes it is noticeable that the cells have increased in size as well as in number, and forms have been described which correspond more closely with the larger leucocytes of the blood than with the small lymphocytes. Metastasis may occur from primary disease of the lymphatic gland and may involve the other lymphatic structures, the liver, the kidneys, and other organs as in the cases beginning in the spleen or bone marrow.

There is no sharp dividing line by which the changes which affect the lymphatic glands in leukæmia can be separated from those in pseudoleukæmia and constituting what has been variously termed lymphadenoma, lymphosarcoma, and malignant lymphoma. According to Birch-Hirschfeld the only differences found are that the cells are rather larger and often multinuclear or even actually of the type of giant cells in pseudoleukæmia; that attempts to inject substances held in suspension into the gland through the punctured capsule meet with failure in pseudoleukæmia, while in leukæmia the substances injected may pass through the gland even into the efferent lymphatic vessels. Finally, penetration of the capsule and involvement beyond the confines of the gland are more characteristic of Hodgkin's disease. These differences, however, are really slight and

often cannot be determined. Practically the lymphatic lesions of the two diseases are identical.

Cases have been described in which the lymphatic glands as well as the diseased portions of the spleen and of other organs secondarily involved have presented the yellowish-green appearance characteristic of chloroma. Such cases have been studied by Waldstein, von Recklinghausen, and lately by Dock.

Thymus Gland.—Alterations in the thymus gland are frequently observed. Usually the changes consist of nodules of lymphoid appearance or of uniform infiltrations of the gland. Virchow called attention to the persistence of the thymus and to the occasional occurrence of quite marked enlargements of the organ. In a few instances the pathological process has seemed to begin in the thymus gland, manifesting itself in the form of a progressively increasing tumor having the general appearances and the histology of lymphosarcoma. In such cases direct extension or secondary involvement of the mediastinal glands is prone to be met with early, while universal metastasis occurs secondarily.

Thyroid Gland.—Lymphoid infiltration and nodular involvement of this gland have been observed, but are unusual.

Gastrointestinal Tract.—Attention has been called to the involvement of the lymphoid structures of various parts of the gastrointestinal mucous membrane. The follicles at the base of the tongue and the tonsils may be among the earliest seats of disease, becoming enlarged and presenting the white color and the general appearance seen in the lymphatic nodes. Throughout the gastrointestinal tract similar nodules of lymphadenoma are met with. In the stomach there may be flat elevations with surface ulcerations. In the intestines the solitary follicles are frequently enlarged and small erosions or ulcers are prone to occur. The Peyer's patches may be considerably swollen and ulcerated, presenting a close resemblance on superficial examination to the ulcers of typhoid fever. While the lesions of the intestines are for the most part found to involve the normal lymphatic follicles, nodules may occur independently and in situations where lymphoid tissue had no previous existence.

Ulceration of the mouth and other forms of stomatitis frequently occur in the earlier stages or throughout the course of the disease. These lesions appear to be particularly frequent in the acute forms of the malady. Ulcers in the lower parts of the tract are rarely met with, excepting in connection with the lymphomatous enlargements.

Skin.—Lymphatic nodules or diffuse hyperplasia of the skin have been described and in some cases the dermal involvement seems to be the predominating pathological condition. The lesions may begin

as a more or less uniform eczematous condition, leading to a lichenoid appearance in its further development and finally to the formation of distinct swelling or tumor-like formations with ulceration. The condition in its final state is that designated as mycosis fungoides. Dermatologists and pathologists are by no means united in regarding these conditions as leukæmic and in only a few cases was the condition of the blood suggestive.

Sometimes the lesions of the skin are distinctly those of prurigo, though certain differences have been pointed out.

Serous Membranes.—The serous sacs frequently contain a certain amount of liquid transudate having a light straw color or, more rarely, of reddish appearance due to admixture of blood. Nodular lymphoid deposits or diffuse thickening may occur in the membranes themselves. In the pericardium the lymphomata are found in the subepicardial tissue especially along the blood-vessels. In the peritoneum the nodules may be disseminated throughout the entire abdomen as in the case of Laache, or may be confined to a single portion, as in the case in which Birch-Hirschfeld recorded the involvement of the mesocolon. Considerable thickening of the pleura has been observed and the membrane has been found in some cases studded with nodules (Friedreich, Mosler).

Liver.—Enlargement of the liver is usually an early manifestation of leukæmia, especially in cases in which the spleen is implicated. The size may be exceedingly large and the weight has been found as great as 10 kgm. The surface is usually smooth, the edges distinctly rounded, and the substance generally quite hard. On section the appearance presented is found to be quite variegated, the normal liver substance being mottled with areas of light color or marked with a fine network of streaks or lines. In the latter cases the light-colored areas are found surrounding the acini whose outlines thus become distinctly marked. The pressure of the infiltrating lymphoid tissue may cause serious compression and atrophy of the hepatic lobules so that spots of pigmentation alone indicate their former existence. In less advanced cases fatty degeneration of the liver cells occurs in consequence of the pressure. Microscopically it is found that the infiltration occupies the periportal structures and the peripheral zones of the lobules surrounding the intralobular capillaries. In the cases in which nodular masses are seen with the naked eye the microscope shows that they are periportal in situation or origin. The small blood-vessels are found densely packed with leucocytes, while the perivascular tissues are infiltrated to varying distances around. M. Smidt, and more recently H. F. Müller, have called attention to the return of the liver

structure to the fœtal condition, and the former has expressed the view that the hæmopoietic function of embryonal life is reestablished. Müller noted the frequency of mitoses in the corpuscles in the hepatic capillaries.

The lymphatic glands in the fissure of the liver are generally enlarged and may reach considerable size.

Chemical examinations of the liver made by Salkowski showed a peptone-like substance in small proportion, tyrosin and leucin in considerable quantity, xanthin bodies and succinic acid but no uric acid. Bockedahl and Landwehr found considerable peptone (?), leucin and tyrosin, xanthin, succinic acid and lactic acid. Hypoxanthin and uric acid were absent.

Kidneys.—Involvement of the kidneys is frequent. The infiltration usually begins at the cortex and extends inwards. It may be diffuse or in lines; or, on the other hand, quite distinctly nodular, the nodules at times becoming of large size and presenting a vascular or hemorrhagic character. The infiltration is mainly found surrounding the tubules and the Malpighian bodies. The nodules, as elsewhere, present a fine reticulum containing round cells within its meshes. Uric-acid infarcts of the tubules have been described by Virchow. The parenchyma of the kidneys may suffer considerable parenchymatous or fatty degeneration in consequence of the pressure, and amyloid disease has been occasionally noted.

The suprarenal bodies are frequently involved and occasionally become quite large. A case is recorded by Fleischer and Penzoldt in which the size was so great that rupture occurred.

Respiratory Tract.—Infiltration of the mucous membrane of the epiglottis, the trachea, and the bronchi is not unusual. Small nodules from 1 to 2 mm. in diameter and closely resembling tubercles in their appearance (Virchow) are observed. Considerable involvement of the lungs themselves (Deiters) may occur and the infiltrated areas may suffer necrosis and break down with the formation of cavities resembling those of tuberculosis (Böttcher).

Heart.—The cavities of the heart are usually only moderately distended and the left side frequently is quite empty. Light-colored clots are commonly observed, and sometimes the chambers of the heart contain blood presenting an appearance not unlike sanious pus. At times the opening of the heart seems like an incision into an abscess. The muscle substance is pale and not rarely light areas of fatty degeneration are apparent. Extreme fatty degeneration is unusual but may occur in the advanced stages of the disease. Lymphoid infiltration between the muscle fibres and punctiform hemorrhages in the myocardium are more specific and characteristic

lesions. Acute vegetative endocarditis was found post mortem in one of my cases, and has been repeatedly observed by others.

The salivary glands are less frequently involved than other organs. A number of cases have been described, however, in which the parotid gland has been a striking situation of lesions, as in the instance recently reported by Dunn.

The Eyes.—Nodules have been found in the orbits by Birk and others. Considerable tumors may thus be formed around and behind the eyes. Ophthalmological examination shows the vessels of the retina to be large and tortuous and infiltrations may be visible about the adventitia; the smaller vessels may be obstructed with masses of leucocytes and their walls may suffer fatty degeneration. Whitish areas of thickening and sclerotic change and areas of fatty degeneration may be striking features. Nodular or diffuse infiltrations of the iris and the choroid have been observed.

The brain and meninges may be infiltrated and hemorrhages sometimes occur. The vessels of the brain and the perivascular lymphatic channels are densely filled with leucocytes, and in the cases of hemorrhage the blood mass may be largely composed of white corpuscles. The spinal cord may present degenerative lesions resembling those seen in pernicious anæmia (Minnich).

Bones.—Rarefaction of the bones has been referred to by some and osteosclerosis has been found by Hauck. Chemical analysis of the bones made by Bockedahl and Landwehr has shown a considerable proportion of peptone (?).

The Blood.

The most characteristic changes of leukæmia are found in the blood.

When the finger or some other portion is punctured the blood oozing from the surface may present striking peculiarities. Sometimes it is simply light-colored and perhaps more fluid than normal. At other times it resembles lymph or may be of such whiteness that it is quite milk-like or puriform. At times the color is dark, and in certain cases it has been likened to chocolate. Usually there is no difficulty in obtaining it freely from the punctured finger and not rarely the flow is abnormally active. Occasionally there is a decided hemorrhagic tendency and it may be difficult to cause the bleeding to stop.

The specific gravity is generally diminished and has been found to vary between 1036 and 1049.

The reaction is alkaline as in normal blood, though of a lesser degree, and there is a tendency to rapid decomposition after removal

from the body, with the development of an acid reaction. This is probably due to decomposition of lecithin with the production of glycerophosphoric acid. Various acids, such as lactic, acetic, formic, and succinic, have been found in the blood, but an acid reaction is never detected in the fresh blood, as was at one time believed by some.

Most observers have been struck by the fact that the blood as it escapes from the body does not coagulate as readily as normal. Samson-Himmelstjerna has studied this in particular, while Bockedahl and Landwehr and Freund, in calling attention to the same fact, suggest that the presence of peptone (?) in the blood leads to this decreased coagulability. Rywosch and Berggrün found that the coagulation is rendered more rapid or normal when the blood is treated with carbonic-acid gas, these experiments having been suggested by Fano's assertion that blood containing peptone may be restored to normal coagulability by such treatment, while normal blood is rendered less so. Wright has confirmed the latter observation.

Allusion has already been made to the character of the clots found within the cardiac chambers and in the vessels in leukæmia. When the blood is allowed to coagulate outside the body it is noticeable that the lower portion of the clot containing the red corpuscles is comparatively insignificant, while the upper light-colored portions composed largely of leucocytes is of considerable amount. Firm clotting is unusual within the heart, but there is usually semi-solidified puriform material instead. In the smaller vessels white clots occur, and owe their development to the fact that the white corpuscles circulate with less freedom than the red and that in consequence stasis is prone to occur.

The Leucocytes.—The microscopic examination of the blood discovers the most characteristic feature of the disease, viz., the increased number of leucocytes. In cases of moderate severity there may be 100,000 or 200,000 white corpuscles per cubic millimetre, while in severe cases 500,000, 1,000,000, or even a greater number may be observed. The relation of the number of leucocytes to the number of red corpuscles is enormously disturbed, so that in severe cases a proportion of 1 to 2 or 1 to 1 may be seen and the number of leucocytes may be actually double that of erythrocytes (Robin). The actual number is more important than the proportionate, as the variation in the number of red corpuscles plays an equal part in the alteration of the relation with the number of the white corpuscles. Among the older writers the proportion, however, was considered important, and a distinction was made between leucocytosis and leukæmia according as the relation of white to red was below or above 1 to 20, 1 to 50, or some other adopted standard. Such a distinction,

however, cannot now be maintained. Cases of undoubted leukæmia occur in which the actual number of white corpuscles is not greatly increased and in which the relative proportion is but little disturbed, while on the other hand instances of leucocytosis may be cited in which the relation of white to red corpuscles may be as great as 1 to 2. Even quite recently, however, certain authors have adhered to a numerical distinction between leucocytosis and leucocythæmia, although they admit that such a distinction is by no means absolutely reliable. Thus Gilbert (following Hayem) places the limit of leucocytosis at 70,000.

The number of leucocytes varies considerably from time to time in consequence of surrounding conditions or of disease. The influence of infectious diseases in particular is of interest. Eisenlohr reports a case in which the supervention of typhoid fever caused great reduction in the number of corpuscles, while Quincke observed the same in consequence of acute miliary tuberculosis, and Stinzing made a similar observation. Kovacs saw a decided decrease following influenza, Müller following sepsis, and Fraenkel after a similar disease. In these cases there is some alteration in the character of the leucocytes as well as in the number, the mononuclear elements suffering great decrease, while the polynuclear forms become relatively more numerous. A decrease in the number of leucocytes may, however, occur without distinct cause. In a recent case I have seen fluctuations amounting to 25,000 to 50,000 on successive days in a case in which the total number, on an average, was about 300,000. Sometimes the number suddenly or quite rapidly falls almost or quite to the normal, and examination of the blood may no longer reveal the nature of the disease excepting possibly on careful study of the characters of the individual leucocytes. Thus in a case studied by Thayer the number of corpuscles under treatment became almost normal, though the relative excess of large mononuclear forms containing neutrophilic granulations (myelocytes) still gave evidence of the nature of the disease. In a case under my own observation the number of leucocytes fell rapidly from 150,000 to 30,000, though the symptoms continued with but little alteration.

Certain peculiarities of the nature of the leucocytes in general have been observed and recorded. According to Hayem the number of white cells containing small quantities of hæmoglobin is greatly in excess of the normal, this observer holding that in normal conditions a certain number of white corpuscles contain this coloring matter. In cases in which leukæmia has followed chronic malaria it has been pointed out that many of the leucocytes contain notable quantities of pigment matter.

Amœboid Movements.—Biesiadecki, in studying a case of myelogenous leukæmia in 1876, called attention to the fact that the amœboid movements were strikingly sluggish. In particular he noticed that while the movements of the corpuscles having about the size of red corpuscles or slightly greater size were active, those of the corpuscles from two to four times the size of the red corpuscles were greatly decreased or entirely wanting. Later observations were made by Neumann (1876), Cavafy (1878), Renaut, Löwit, and more recently by Müller and Rieder. All observers have noted that practically all of the cells of the largest size are almost or quite devoid of movement, while the polynuclear or polymorphous cells present the same amœboid activity as those of the normal blood or of leucocytosis. Some difference of opinion has been expressed regarding the smaller mononuclear leucocytes, though it is quite evident that movements are usually sluggish or absent. The increased number of large mononuclear cells in lienomedullary leukæmia gives rise to the impression that the blood is devoid of amœboid movement, whereas in reality the cells which normally possess contractile powers are as active in leukæmia as in health. Müller and Rieder, however, insist upon the value of these amœboid movements as indicating leukæmia, holding that the large cells presenting no amœboid movement at all are peculiar to this disease. The study of the individual forms of leucocytes has received a powerful impetus during recent years by the masterly investigations of Ehrlich and his pupils and has been rendered especially easy by the introduction of the dry method of fixation suggested by this investigator. As Müller has pointed out, nearly all of the essential points in the histology of the blood known at the present day were observed and described with more or less accuracy by the early observers and notably by Virchow; but the more general knowledge of the disease and the more accurate determination of certain problems are due to Ehrlich's methods.

Virchow distinguished two forms of the disease: The first is characterized by the preponderance of small white corpuscles, resembling those seen in the lymphatic glands; this he designated as lymphatic leukæmia or lymphæmia, the same form being spoken of as small-celled (*kleinzelliche*) leukæmia by Kottmann. The second form is characterized by the greater proportion of cells of large size such as have been discovered in the spleen, and this variety was therefore called lienal leukæmia or splenæmia by Virchow and large-celled (*grosszelliche*) leukæmia by Kottmann. Later the investigations of Mosler, Neumann, and others made it clear that involvement of the bone marrow is important in certain cases, and the existence of medullary or myelogenic leukæmia was thus established. At the present

time it is generally acknowledged that cases of leukæmia rarely involve one only of the blood-making structures, coincident disease of two or more being the rule. The most frequent variety, as has already been indicated, is the combined splenic and myelogenous (the lienomedullary form). Next in frequency are the cases in which the

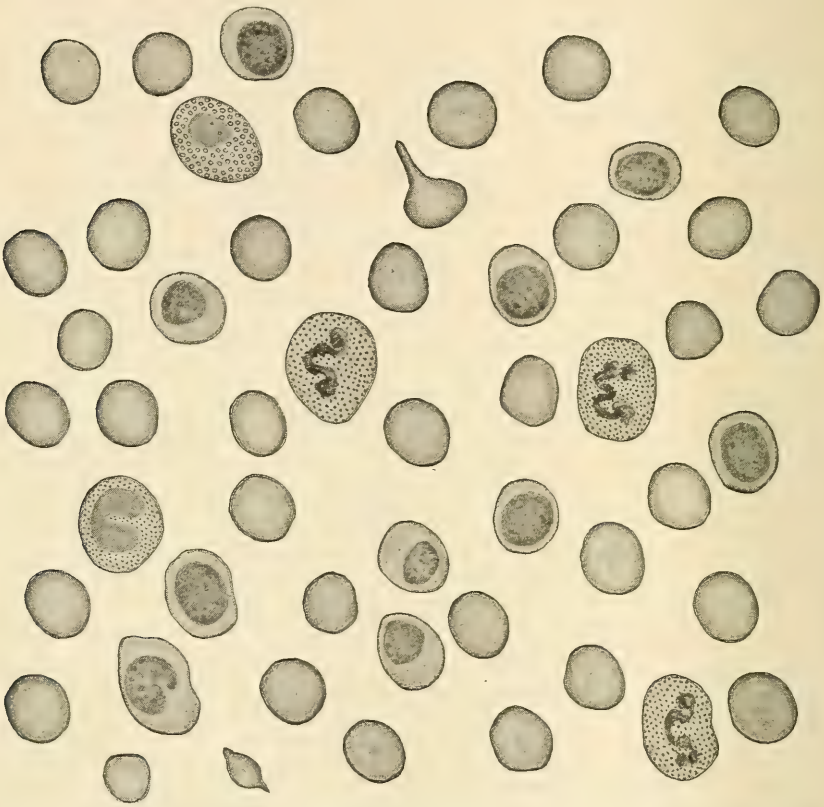

Fig. 39.—Lymphatic Leukæmia; Lymphæmia. Showing excessive numbers of small mononuclear leucocytes or lymphocytes.

lymphatic glands are involved to the exclusion, or at least to the practical exclusion, of the spleen and bone marrow. For practical purposes these two varieties, the lienomedullary and the lymphatic, may be admitted as representing the important pathological varieties, and the condition of the blood serves to establish the existence of the one or the other with more or less certainty. It will be well now to consider the individual forms of leucocytes as they are met with in this disease. In this consideration the classification of Ehrlich is followed.

Lymphocytes.—These forms are small mononuclear leucocytes,

having a nucleus rich in chromatin and which therefore stains intensely with the nuclear stains. The size is usually less than that of the red corpuscle, though they are occasionally slightly larger. The nucleus almost fills the cell and the protoplasm is free of granular matter. It may be so scanty that the corpuscle at first presents the appearance of a free nucleus. The lymphocytes are greatly increased in number in cases of lymphatic leukæmia (lymphæmia). In such cases the increased number of white corpuscles may be almost entirely due to excess of lymphocytes. The latter show no striking alterations from the characters as seen in normal blood. Evidences of cell division (karyomytosis) are rarely observed. Sometimes, however, the lymphocytes differ from the normal in containing granulations, particularly the coarse basophilic granules or mastzellen granulations of Ehrlich. I have also seen them densely filled with neutrophilic granules.

In a recent study of cases of acute leukæmia Fraenkel called attention to the presence of certain cells in the blood which differed from the ordinary lymphocytes in being considerably larger, many of them twice the size of the ordinary red corpuscle and having a large and sometimes bipartite or polymorphous nucleus, relatively poor in chromatin. These cells he regards as of lymphatic origin and points out that he found them abundantly in the lymphatic glands post mortem. The actual relation of these leucocytes is uncertain, though the possibility of their being lymphocytes pathologically enlarged is entertained, and Fraenkel refers to the statements of Virchow and of Birch-Hirschfeld that the cells of the lymphatic glands increase in size as well as in number in leukæmic disease of these structures.

Large Mononuclear Leucocytes.—These forms have been characterized by Ehrlich as leucocytes considerably larger than red corpuscles, having a large rounded nucleus but small in comparison with the size of the cell. The nucleus is poorer in chromatin than that of the lymphocyte and the protoplasm is usually free of granules. In leukæmia these cells are of comparative unimportance, though they are considerably increased in number in certain cases of the lienomedullary type. In lymphæmia they are relatively much reduced in number.

Transitional Leucocytes.—These differ from the last only in the fact that the nucleus is irregular in outline. Occasionally neutrophilic granules have been found in health. The relation of these cells to leukæmia is much the same as that of the large mononuclear cells; indeed, no sharp dividing line can be drawn between these forms. These two forms will be more appropriately considered in the following section.

Myelocytes or Markzellen.—Mosler first called attention to the occurrence in a case of leukæmia of certain large mononuclear cells, the origin of which he was able to trace to the bone marrow by puncturing the sternum and demonstrating the presence of similar cells in the liquid so obtained. Other observers have recorded observations upon

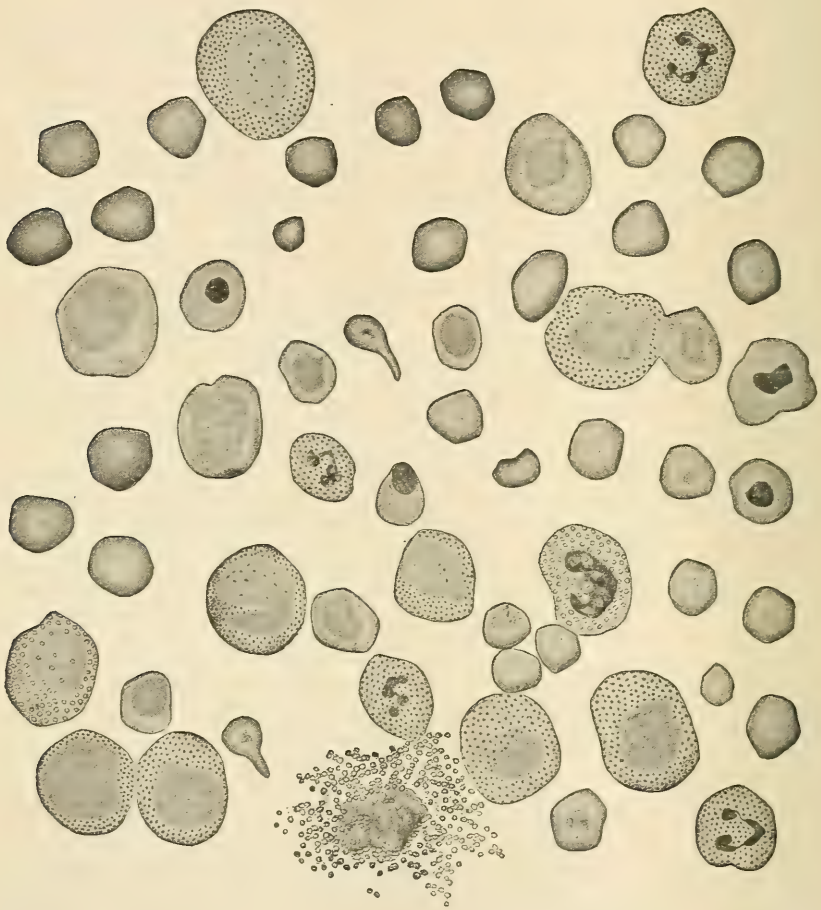

FIG. 40.—Lienomedullary Leukæmia. Showing poikilocytes and nucleated red corpuscles and leucocytes of various types, many being large mononuclear forms containing neutrophilic granulations (myelocytes). One broken eosinophile cell in the lower part of the field.

the blood of a similar character. Thus Uhle called attention to certain very large cells in 1853 and Eberth (1868) referred to leucocytes of unusual size with nuclei poor in chromatin. Neumann had previously described marrow cells having the general appearance of those discovered in the blood by Mosler, and on examining the speci-

mens from Mosler's case pronounced the cells in the blood as morphologically identical with those described by himself in the marrow. Subsequently a number of authors (Eisenlohr, Grohe, Litten, Heuck, and others) have referred to the same structures. Cornil and Robin described cells under the name of *cellules médullaires* and *médulocelles* which Müller identifies with the cells of Mosler and of later authors. Ehrlich and his pupil Uthemann described the same form and determined its characters by the modern methods. The cell of Ehrlich is a large mononuclear form, the nucleus being comparatively poor in chromatin and the protoplasm containing more or less abundant neutrophilic granules. This cell, according to Ehrlich, is identical with the cells containing neutrophilic granules found in the bone marrow, and Uthemann named it definitely the myelocyte. Recently H. F. Müller has discussed the nature and origin of this cell elaborately and has established the identity of the forms described by different authors. The myelocyte, or *markzell* as Müller terms it, is a large body varying from four to five or six times the diameter of the red corpuscle, having an extremely pale nucleus, sometimes with an irregular outline but more usually rounded or oval, lying in the centre or often towards one side of the cell. The protoplasm of the myelocyte usually contains granulations staining with the neutral mixtures of Ehrlich, but in certain cases the granules are oxyphilic or eosinophilic, as Wertheim, Müller, v. Jaksch, and others have determined. Finally, it is the myelocytes in particular which are devoid of amœboid movement, the cells lying stiff and motionless upon the warm stage.

The nature of this cell still remains doubtful. According to the earlier observers it was identical with the cells of the bone marrow, although no special attempt was made to determine its relations with the leucocytes of the circulating blood. The authors who hold to the theory that leukæmia is essentially a disease of the blood itself (Biesiadecki, Löwit, and others) look upon it as a form of leucocyte or a cell related in some way to the leucocytes and not as a distinct cell form. The lack of amœboid movement suggested to Birch-Hirschfeld that it is a large and degenerated leucocyte, while Löwit, though not denying the resemblance to the marrow cells, holds that the identity of these with the myelocytes of the blood has not been established. Ehrlich and some of his followers, though pointing out the resemblance or identity of these cells with those of the marrow, have not denied a relationship of these to the leucocytes. The myelocyte, however, was regarded by them as a form never seen in the circulating blood excepting in leukæmia. The French writers, notably Renaut, Hayem, and Gilbert, look upon these cells as hypertrophic

leucocytes, though the latter author points out their variation from ordinary leucocytes in size, in the lack of chromatin, and in the absence of amœboid movements. Müller advocates very strongly the entire distinction of these cells from the leucocytes and regards them as identical with the cells of the marrow, explaining their presence in the blood by the assumption that they are carried into the circulation as are the nucleated red corpuscles. It must be admitted on careful study of these cells that in their morphology and vital properties they are identical with the cells of the marrow, but it has not as yet been shown that the latter cells are distinct formations in no wise comparable with leucocytes, and exception may properly be taken to the view of Müller that the myelocytes are distinct formations. Proof is required in support of this distinction, since in their general appearances the markzellen and certain cells of the blood differ only in certain perhaps unessential features. In this connection the cells mentioned by Fraenkel and found so abundantly in the lymphatic glands may again be referred to. These cells differ widely from the cells of the lymphatic glands and from the ordinary lymphocyte, yet their origin from the glands is at least probable. The life history of the leucocyte is still veiled in deep obscurity and it is not impossible nor perhaps improbable that a certain phase is found in the marrow cells, and that though this period may normally display itself only within the marrow, abnormally the marrow cells may be carried into the circulation.

The marrow cell is a constant and striking feature of the blood of lienomedullary forms of leukæmia, though it also occurs in small numbers in cases in which the lymphæmic type is in other respects conspicuous. In some cases the number is striking, fully twenty or thirty per cent. of the total number of the colorless cells being of this form.

Eosinophile Leucocytes.—The earlier writers (Virchow, Vogel, Friedreich, and others) call attention to the occurrence in leukæmia of certain large cells containing fat droplets. These were referred to by Max Schultze as *grobgranulirte Zellen.* They were more minutely studied by Ehrlich, who found the granules possessed of particular affinity for the so-called acid stains and especially for eosin. The latter were, therefore, designated eosinophile granules. The careful microchemical studies of Ehrlich showed beyond question that these granules or spherical bodies are not oil drops, as was held, and the studies of Weiss and Posner have made it extremely likely that they are albuminous in nature. Litten maintained that he had stained these granules black with osmic acid, and Müller confirms this observation, though he at the same time denies the sufficiency of this

as evidence of their fatty nature, quoting Heidenhain that as "all is not gold that glitters, so all that stains black with osmic acid is not fat." The studies of Barker and Przewoski suggest that these granules contain iron.

Ehrlich laid great stress upon the importance of these cells in leukæmia, basing this view upon their abundance in the marrow. Subsequently, however, it has been found that increased numbers of leucocytes containing oxyphilic granules may occur in the blood in health (in the new-born) or in various diseases (asthma, skin diseases, nervous diseases), while on the other hand cases of lienomedullary leukæmia are frequently seen in which the relative number of eosinophile corpuscles is not increased, and in which indeed their number seems diminished. Sometimes the proportion in leukæmia rises to fifteen or twenty per cent. in comparison with the normal of from one to ten per cent., according to various observers; and on the other hand, the proportion very frequently is not above two to five per cent.

Recent observers are united in denying any special significance to these granules. They may occur in the markzellen, but more commonly in polymorphous cells or in mononuclear cells with comparatively dark nuclei and presenting some amœboid movement. Occasionally lymphocytes present eosinophile granules.

Polymorphous or Polynuclear Leucocytes.—The polymorphous leucocytes tend to decrease in number in all cases of leukæmia as they tend to increase in most forms of leucocytosis. Sometimes the number is extremely small, falling from the normal of sixty or seventy per cent. to twenty, ten, or even one per cent. of the total number of white corpuscles. Wide variations sometimes occur in the appearance of the nucleus, and in some cases I have been struck by the fact that the chromatin of the nucleus of some was distinctly less marked than in the normal blood and much more irregularly distributed, while in others the normal appearance or even abnormally abundant chromatin was observed. The neutrophilic granules characteristic of these cells in the normal blood may be present as in health, but all observers who have studied the blood of leukæmia have noted the occasional entire absence of the granules. More commonly the granules are less abundant and less sharply defined than in normal blood. Sometimes oxyphilic granules are observed. The supervention of some form of infection may cause a reduction in the total number of leucocytes in the blood, as has already been observed, and at the same time the polynuclear forms may become relatively more abundant. The same change occurs when the number of leucocytes diminishes under treatment.

In studying the blood of leukæmic cases the nuclear alterations are always striking and in particular the tendency to a decreased richness in chromatin. The peculiar pale and often irregular nucleus of the myelocytes is most conspicuous, but in all of the forms similar changes are noticeable. Very recently Gumprecht has called particular attention to this and holds that it is an evidence of transformation of the nuclein compounds of the nucleus into xanthin bodies.

Karyomitosis.—Important facts in the pathology of the disease have been added by the discovery of leucocytes presenting karyokinesis. These were first demonstrated by Flemming, but were subsequently observed by Arnold, Hayem, Spronk, Müller, Wertheim, and others. Usually the number of leucocytes of this character is extremely small, and Flemming states that he saw but one among a number of thousands of white corpuscles. Mitotic figures may be found in any of the leucocytic forms, but according to Müller they are especially frequent and significant in the large mononuclear elements or myelocytes. Earlier observers refer to the occurrence of evidences of nuclear division (Kottmann, Renaut, and Biondi); but the evidence that these were actually leucocytes undergoing mitosis and not merely polymorphous or fragmental nuclei may be doubted. It has been denied by certain observers that karyokinesis of the leucocytes occurs at all, and Löwit and Biesiadecki in particular hold this opinion. The positive observations referred to, however, make the matter certain, and there can be no doubt at all in the mind of one who has studied leukæmic blood according to the modern methods.

Fig. 41.—Leucocytes Showing Karyokinetic Figures.

The *red corpuscles* in leukæmia present only secondary alterations. Their number may be entirely normal, or indeed at times there may be an excessive proportion (Quincke, Litten, Waldstein). In almost all advanced cases, however, a reduction in the number of red corpuscles may be observed. In the majority of cases this reduction is moderate, the number falling to 3,000,000 or 2,000,000 per cubic millimetre. In severe cases there may be but 1,000,000, while extreme instances are recorded where the number has been 301,000 (Suchanek) and 316,000 (Eichhorst).

The character of the red corpuscles alters progressively with the reduction in number. The form may vary from slight deviations to

the most extreme grades of poikilocytosis; and oval, lanceolated, irregular, or apparently fragmented forms may occur in varying proportions. The color of the corpuscles does not vary largely from the normal and their behavior towards stains may be entirely normal, though Troje and others have called attention to the fact that they may exhibit striking polychromatophilia. Nucleated red corpuscles were first discovered by Neumann and have subsequently been seen by most of the investigators. The majority are about the size of a red corpuscle or even much smaller, belonging to the group of normoblasts of Ehrlich. Extremely large nucleated corpuscles (megaloblasts) are, however, not unusual and may sometimes occur in considerable proportions. The total number of nucleated red corpuscles may be small, but at times increases greatly (a thousand or more per cubic millimetre); they are most abundant in the lienomedullary form. According to Ehrlich they are particularly significant of involvement of the marrow. In the lymphatic type they are less abundant and were entirely absent in cases observed by Wertheim, Hayem, Neumann, Rieder, and others. In acute leukæmia they are usually scanty and may be wholly wanting.

Friedreich called attention to the fact that the red corpuscles sometimes present amœboid movements, as has been observed more particularly in pernicious anæmia by later observers.

The hæmoglobin falls in percentage with the decrease in number of corpuscles and often declines more decidedly than the latter. In severe cases the percentage varies from thirty to twenty, or even fifteen.

Charcot Crystals.—Charcot first discovered certain crystalline formations in the blood of leukæmia after death. Subsequently they were found in the blood as well as in the juice of the spleen during the lifetime of the patient by Westphal, Ord and Copeman, and others. The nature and origin of these crystals, whose identity with the crystals found in the sputum of asthma by Leyden is generally accepted, still remain more or less in doubt. According to C. Vulpian they are octahedral formations having a length of about 0.04 mm. and a width of 0.006 to 0.008 mm. They are usually demonstrable only after the blood has been allowed to stand a certain length of time and to suffer a certain amount of inspissation. They may occur singly or in the form of radiating, star-like groups. Cohn has lately described them as hexagonal pyramids. Their origin has been supposed by some to be from substances found in the plasma, but others regard them as derivatives from leucocytes, and occasionally they have been found within the leucocytes themselves. In a preparation of blood from a case of pernicious anæmia shown me by Prof.

Frederick P. Henry the leucocytes were all indistinct and formed the centres from which radiating clusters of Charcot crystals took their origin.

The same crystals are found within the normal marrow, but with particular abundance in the pyoid marrow of leukæmia (Neumann). Their chemical composition has been determined by Schreiner to be a phosphate of an organic base. The crystals have been supposed to be identical with the spermin crystals of Böttcher, but recent investigations point to differences in crystallography and in refractive behavior. They are never abundant in the blood and a number of observers have looked for them in vain.

Certain atypical and more or less doubtful cell forms have been described by a number of observers. Thus Virchow described certain cells presenting an attenuated tail-like extremity (*geschwänzte Zellen*). These were subsequently described by Vogel, Lücke, and Wertheim, the latter pointing out that they occur only in the lienomedullary form and regarding them as probably allied with the spindle cell found in the blood of cold-blooded animals by v. Recklinghausen.

Occasionally the leucocytes contain red corpuscles or fragments of red corpuscles.

Blood Plaques.—The blood plaques are sometimes strikingly numerous, large groups being found scattered among the other corpuscles. Prus in his investigation found 2,000,000 per cubic millimetre as compared with 500,000 or less, the normal number. In other cases the number seems reduced.

Chemical Alterations in the Blood.—The older authors claimed that peptone was a constituent of the blood in leukæmia, and even recently similar findings have been reported. Among others Ludwig, Freund and Obermayer, and v. Jaksch have recorded this condition. More recent knowledge, however, makes it most likely that peptone in the sense of Kühne does not occur and that the substances supposed to be peptone are in reality albumoses. Mathes found deuteroalbumoses in two cases in which the blood was examined after death, but it is probable that these substances as well as the supposed peptone of others are due to post-mortem alterations, as the examinations of all of these investigators were made after death. Von Limbeck showed by studying the blood immediately after removal from the body and after twenty-four hours that albumoses were developed in notable quantities, though absent in the fresh blood. Mathes has also found neucleoalbumin in the serum. Undoubtedly this resulted from leucocytic destruction with liberation of the nuclear substance.

Uric acid has been repeatedly discovered in notable quantity, and

Klemperer in particular found a quantity amounting to 0.0985 per cent. Lecithin may be present in considerable amounts. The xanthin bodies are present in much greater abundance than in health or in other diseases.

Reference has already been made to the occurrence of lactic, acetic, and other acids in the blood.

Analyses of the ash made by Freund and Obermayer showed that the potassium, chlorine, calcium, and magnesium are diminished, while sodium and phosphoric acid are increased. These differences in the composition of the ash are dependent upon the relative decrease in the red corpuscles and the increase in leucocytes, as analyses of pus would indicate.

The distinction of different forms of leukæmia can be made with a certain amount of accuracy by the examination of the blood, though too great a reliance must not be placed on these features, as indicating actual limitations in the pathological processes in the solid organs.

Lymphæmia.—In the lymphatic leukæmia of Virchow the excessive number of small mononuclear leucocytes is striking, the proportion in a remarkable case of Uthemann being ninety-three per cent. of all the leucocytes. Mitoses are rare in such blood and nucleated red corpuscles are exceptional, or at least are never present in large numbers; they have, however, been found by Wertheim, Müller, and Limbeck. Large mononuclear cells corresponding to the type of markzellen rarely occur, though there may be numbers of mononuclear leucocytes larger in size than the ordinary lymphocyte and differing from it in certain peculiarities (Fraenkel). The red corpuscles decrease in number and sometimes rather rapidly; while the degree of leucocytosis is rarely as great as in the lienomedullary form. Limbeck points out the striking resemblance of lymphæmic blood to that seen in lymphosarcomatosis, noting that the only practical difference is the greater degree of leucocytosis in leukæmia.

Lienomedullary Leukæmia.—The most obvious feature in the blood in this form is the preponderance of large mononuclear elements. The myelocytes or markzellen sometimes reach notable proportions and speak for involvement of the marrow rather than of the spleen. The number of lymphocytes, though increased, is less decidedly augmented than is that of the larger mononuclear elements, among the latter being included the mononuclear forms of the normal blood as well as the abnormally large forms or myelocytes. Ehrlich first insisted upon the value of eosinophile corpuscles as indicative of a myelogenic form of the disease, but this view is no longer maintained. Deduction may be formed with much greater certainty from the pres-

ence of nucleated red corpuscles, the occurrence of large numbers of such pointing with considerable probability to myelogenous involvement. The discovery of Charcot crystals in abundance may further be taken as contributory evidence; while the absence of neutrophilic granules in the polymorphous leucocytes and the occurrence of nuclei poor in chromatin in the latter are further points of value.

Pure splenic leukæmia probably rarely if ever occurs, and cannot be distinguished by the blood. The preponderance of large mononuclear or transitional corpuscles has been said to point in this direction; but this view cannot be maintained.

Pathogenesis.

Investigators are divided into two groups by the views taken of the pathogenesis of this disease. The larger number hold to the theory of Virchow that leukæmia is primarily a disease of the blood-making organs and that the condition of the blood is secondary. The smaller group maintain that the primary disease resides in the blood, while the organic lesions are secondary. The theory of Virchow rests upon the discovery of organic changes in the organs recognized as having relation to the formation of blood, and upon the fact that these changes are regarded as actually proliferative in character. Virchow maintained that the excessive number of the leucocytes was due to overproduction in the solid organs and the retardation of the normal conversion of leucocytes into red corpuscles within the same organs. Neumann was practically of the same opinion, though differing somewhat in his views regarding the formation of red corpuscles. Klebs and the last-named author refer particularly to the occurrence of nucleated red corpuscles, looking upon these as evidences of a slower transformation of white into red cells. Later writers have taken different views regarding the formation of red corpuscles, and the origin of these is now quite generally believed to be independent of the leucocytes. Nevertheless the opinion still remains fixed that leukæmia results from primary disease of the blood-making organs with overproduction of leucocytes. Doubt was cast upon this view by those who adhered to the theory that leukæmia is a primary blood disease, and in particular by their assertion that the changes in the organs result entirely from deposit of the circulating leucocytes within these structures and not from actual processes taking place in them. This view, however, has been practically disposed of by the discovery by Bizzozero, Wertheim, and others that karyokinetic changes are more or less numerous in the diseased portions of the bone marrow, lymphatic glands, spleen, and other organs.

The occurrence of karyokinetic corpuscles in the circulating blood is further evidence of the overproduction of leucocytes, and in view of the absence of mitosis in the normal blood it is reasonable to suppose that the overproduction occurs in the blood-making organs rather than in the blood itself. It has been objected that the number of karyokinetic corpuscles found in the blood or in the blood-making organs is too small to warrant the belief that the changes in the organs result from hyperplasia. To this it may be replied that there is no doubt on the one hand that some of the alterations of the solid organs result from infiltration and deposit and that it is quite likely, as Flemming and Müller have held, that the production of leucocytes occurs paroxysmally (*schubweise*) and in restricted localities (*localer Auftritt*). It is of some importance to note that M. Schmidt and Müller have found changes in the liver in leukæmia which indicate a return to the fœtal blood-forming function. They refer particularly to the discovery of numerous mitotic figures and nucleated red corpuscles.

Bennett likened the corpuscles to pus cells and spoke of his case as one of suppuration of the blood, at the same time referring to the *hæmitis* of Piorry. Kottmann speaks of the disease as a neoplasm of the blood, while Bard designated it as a veritable *cancer du sang*. Among the other investigators Griesinger and lately Biesiadecki have been prominent. The first-named writer pointed out that he had actually seen evidences of the transformation of white to red corpuscles in the circulating blood and that changes in the blood may antedate the enlargement of the spleen. Biesiadecki regarded leukæmia as a form of retrograde metamorphosis of the blood, the changes in the blood-making organs being the result of filtration deposits comparable to the deposits in the same organs of small foreign bodies introduced into the circulation. He was particularly struck by the absence of amœboid movements in the large white corpuscles, holding this to be an evidence of leucocytic degeneration. The most ardent advocate of the primary origin of the disease in the blood is Löwit. He denies that there is excessive production and holds that the accumulation of leucocytes is due to the slower development and destruction of these cells, and that the occurrence in the circulation of excessive numbers of mononuclear cells is evidence of the arrested development of the leucocytes. While there is some justification for the view that the cycle of development of the leucocytes is altered in leukæmia, evidence is lacking that leucocytic destruction is less active than in health. On the contrary, certain facts point to increased though perhaps not excessive leucolysis. The positive discovery of mitosis in the blood and in the blood-making organs is, however, the

most important fact in disproof of the theories of Biesiadecki and Löwit.

Lately a gastrointestinal origin has been urged. The frequent occurrence of inflammatory and ulcerative changes in the gastrointestinal tract has suggested to some the likelihood of infection occurring from this source. Others have maintained the absorption of chemotactic substances from the intestines and the consequent development of leucocytosis. Vehsemeyer in particular urges the importance of digestive disturbances, and believes that the failure of these organs to convert peptones into their ultimate products is an important causal factor. In experimental work upon dogs he was able to produce a high-grade leucocytosis by solutions of peptone, and ascribes the failure of Löwit to obtain similar results to his having used animals unsuited to the purpose. A similar position is taken by Pawlowski. This observer suggested that leukæmia results from circulation of chemotactic substances which abstract unripe leucocytes from the blood-making organs. The occurrence of mitoses is explained by the assumption that part of the leucocytes thus abstracted complete their cycle of development within the circulating blood.

Despite the views of those who look upon the disease as a primary disorder of the blood, we may conclude that the affection is primarily a disorder of the blood-making organs, the nature of which, however, still remains obscure. In acute cases the possibility of infection cannot be overlooked, though bacteriological studies are as yet entirely unconvincing. In the slow chronic cases it is more difficult to trace evidences of infection, though such is by no means impossible; and in this connection allusion may properly be made to the difference between acute miliary tuberculosis and the chronic forms of this infection. The resemblances of the leukæmic lesions to sarcoma are too striking to be passed unnoticed, particularly in such cases as those in which the thymus gland has been found much enlarged and tumor-like. The ameliorating influence of intercurrent infection upon some cases is an additional fact recalling to v. Limbeck the influence of erysipelas upon carcinoma; and finally, the practical impossibility of distinguishing leukæmia from lymphosarcomatosis in some instances is noteworthy. It is not improbable that leukæmia represents a group of diseases the brunt of which falls upon the blood-making organs, all disturbing hæmogenesis in a similar manner. Certainly the character and course of some of the cases, which for the present permit of no other classification than that of acute leukæmia, present wide variations from the features of the chronic or ordinary form. It is not permissible to assert positively,

as some have done, that such cases are essentially dissimilar from ordinary leukæmia, but it is justifiable to entertain the suspicion that different forms of disease affecting the blood-making structures may bring about clinical manifestations of a similar character.

The theories which maintain that there is a primary disease of the blood itself cannot stand in the light of recent knowledge. So much may be confidently asserted.

Symptoms.

Leukæmia is essentially a chronic disease, though occasionally cases are met with in which the course is rapid or excessively rapid (*leukæmia acuta seu acutissima*).

The onset of the disease is generally gradual and may be so insidious that the earlier symptoms are practically overlooked. In other cases the inception of the disease is abrupt and violent; or after a period of gradual development or even latency sudden and fulminating symptoms may develop and may give the disease an appearance of great acuteness.

The first indication may be increasing pallor, but not rarely this is absent for a long time. Sometimes pain in the region of the spleen is the earliest symptom, while in others the onset is marked by the incidence of fever of obscure origin. Occasionally hemorrhagic manifestations are the initial symptoms. A number of authors have referred to priapism as an early symptom, and in several instances this has continued for a considerable length of time before any other evidence of disease had been noted. Subjective or objective symptoms may be wholly wanting and the first manifestation may be the changed condition of the blood. In acute leukæmia the disease may begin with rigors or chills, with elevation of the temperature, and with the general appearances of an infectious disease. Not rarely such cases commence abruptly with hemorrhagic manifestations.

The appearance of the patient is usually rather striking. In most cases pallor is prominent, but the skin more frequently shows a yellowish or ashen color than the clear whiteness of ordinary anæmia; sometimes moderate jaundice is persistently present. In such cases the skin may present a light lemon-yellow or dusky yellow color and the conjunctivæ and visible mucous surfaces may be similarly discolored. Pallor, however, is not always present, and it is a striking fact repeatedly observed that some cases present a healthy hue of the skin despite advanced changes in the blood. This combination with fulness of the vessels and the preservation of strong pulsations has sometimes led to the expression *leukæmic plethora*.

Specific alterations may occur in the skin and subcutaneous

tissues. These appear in the form of small nodular elevations or as more diffuse thickening with a tendency to ulceration. Such cases were described by Biesiadecki, Hochsinger and Schiff, and more particularly by Kaposi, who employed the term *lymphodermia perniciosa*. The case recorded by the latter author was one which began with a diffuse and generalized eczema terminating in diffuse and nodular infiltration, firm œdematous swelling of the skin, and finally ulceration. The changes in the blood were not noted until this time. Cases of this character have been recently studied by Besnier and Vidal.

Eruptions of an accidental or non-specific character are not rarely met with. Eczema and acne may occur or, in more severe cases, furuncles, pustules, or bullous vesicles. Considerable pigmentation of the face, hands, or flexures of the joints may occur, particularly in instances in which the abdominal organs (spleen, liver, glands) are especially involved; and localized pigmentations due to ecchymoses are not unusual.

Pruritus may occur with or without definite lesions in the skin. Sweating may be little altered from the normal, but in some cases is decidedly increased and at times becomes excessive, especially in the later stages when diarrhœa or hemorrhages have led to rapid loss of strength. Drenching night sweats have been noted (Mosler, Trousseau, Chvostek) and may occasion misinterpretations.

The subcutaneous fat is often well preserved as in other anæmic diseases, although less commonly so than in pernicious anæmia. In the later stages it undergoes atrophy together with the muscles and other tissues. Subcutaneous œdema is often observed and is dependent upon the degree of anæmia. At first there is merely slight puffing about the malleoli or beneath the eyes, and the swelling subsides when the patient is in the reclining posture. Subsequently extensive dropsy or anasarca may occur. Effusion in the internal serous sacs is unusual.

Besides the serous effusions of this character there may be dropsical swelling dependent upon cardiac weakness and a form of peculiar, firm œdema (lymphatic œdema of Bamberger) due to obstruction of the lymphatic circulation. Finally local œdema may result from pressure upon venous trunks by the lymphatic tumors.

Rapidly developing subcutaneous emphysema was noted after death by Schultzen and Stintzing in a case which shortly before death had been marked by a strong cadaverous odor.

Circulatory Disturbances.—Disturbances of the heart's action are frequent and early symptoms depend upon the degree of anæmia. The heart may habitually beat more rapidly than normal, but tends

to palpitate violently upon slight exertion or emotional disturbance. The superficial arteries may pulsate visibly especially during attacks of palpitation, and the veins of the neck not rarely show marked pulsations. Senator refers to a case in which a centripetal venous pulse was seen upon the back of the hand, but this was due to aortic regurgitation resulting from acute endocarditis.

The heart is sometimes displaced in an upward direction by the enlargement of the spleen and liver, and the apex beat may be visible in the fourth or third interspace. Actual cardiac enlargement may be discoverable by physical examination, especially upon the right side. Anæmic murmurs are heard over the base or occasionally at the apex, and organic murmurs due to intercurrent endocarditis have sometimes been discovered. Systolic murmurs in the arteries of the neck may be heard and confused humming bruits are frequently audible in the veins, particularly at the valve of the internal jugular. The pulse is generally compressible, but often has a fair volume. The rate is usually somewhat accelerated, and during attacks of palpitation becomes excessive.

Œdema has been referred to. It is more frequently dependent upon the condition of the blood than upon failing circulation, and rarely becomes extreme.

Respiratory Symptoms.—More or less breathlessness upon exertion occurs in every case in which the degree of anæmia is marked; and this may be accompanied by a slight cough and mucous expectoration. Attacks of dyspnœa may accompany the palpitations or may be independent of such when enlargement of the intrathoracic lymphatic glands causes pressure upon the air passages or the nerve trunks. Intercurrent bronchitis, œdema of the lungs, or pneumonia may occur.

The Lymphatic Glands.—Enlargement of the lymphatic glands may occur before the changes in the blood have become marked, and may be followed by enlargement of the spleen. On the other hand, the condition of the blood may be noted before splenic or lymphatic enlargement has become pronounced. The glands most frequently affected are the cervical chains. These increase more or less rapidly, forming elevated flat swellings beneath the skin or chains running in a longitudinal direction. The submaxillary glands are usually involved at the same time, and the patient complains of a feeling of stiffness in the neck and the head is held firmly in a fixed position. The glandular enlargements are soft in the earlier stages, but in the end may become of almost stony hardness. The skin is usually easily movable; more rarely it becomes fixed, but evidences of inflammatory reaction are scarcely ever observed. The bunches of glands may reach the size of a fist, though they are rarely as large as those

seen in Hodgkin's disease. The axillary groups and those of the groin rank next in frequency, but are not often so greatly enlarged. Swelling of the intrathoracic glands occupying the anterior mediastinum or surrounding the bifurcation of the trachea and bronchi is not unusual, and may give rise to protrusion of the upper portion of the sternum with considerable dulness on percussion. The finger placed in the suprasternal fossa and pressed deeply into the chest may discover the projecting convexity of the enlarged glands in the anterior mediastinum and similar enlargements may be detected beneath the clavicle. Marked symptoms may be produced in such cases by the pressure exerted upon the important mediastinal structures. Nearly always when the glands have undergone notable enlargement there is difficulty in respiration, causing stridulous inspiratory efforts with recession of the suprasternal fossa, of the intercostal tissues, and of the epigastrium; and auscultation may determine that the air enters one or both lungs with great difficulty. Pressure upon the veins may give rise to cyanosis or localized œdema; difficulty in swallowing is noted when the glands of the posterior mediastinum press upon the œsophagus; while attacks of palpitation and of extreme dyspnœa denote compression of the vagus. Hoarseness or aphonia may result from palsy of the vocal cords dependent upon compression of the inferior laryngeal nerve and to a certain extent from direct pressure upon the air passages. Persistence and enlargement of the thymus gland have frequently been noted and sometimes the involvement of this structure is of such magnitude as to constitute a veritable tumor. In such cases pressure symptoms are particularly frequent. Leukæmic involvement of the thyroid is of occasional occurrence.

The lymphatic glands of the abdomen are less prone to enlargement, though the mesenteric and the retroperitoneal groups are sometimes involved. The nodes occupying the fissure of the liver and surrounding the bile ducts may occasion compression of the latter with resultant jaundice. In a few cases the pelvic lymphatics have been involved.

The glands tend to increase in size and in firmness. Occasionally necrosis occurs, but suppuration is extremely rare. Subjective symptoms are usually absent excepting such as are produced by pressure upon surrounding structures. The glands themselves are rarely painful or even tender. Cases of pure lymphatic leukæmia have been recorded, but in most instances some involvement of the spleen sooner or later occurs.

The Spleen.—The first evidence of the occurrence of the disease may be tenderness in the splenic region. This is particularly true of cases in which the onset has followed traumatism in this region,

but it may occur without such. Splenic enlargement is an early symptom, being generally present when the alterations in the blood are discovered and probably in most instances antedating the latter. The organ varies greatly in size so that it may scarcely protrude beneath the ribs; or, on the other hand, may completely fill the left side of the abdomen from the pelvis to the diaphragm, and may project prominently. Ordinarily it is easy to outline the organ by palpation and the notch may be plainly felt in front. The organ is smooth and hard, but at times capsular peritonitis causes a distinctly palpable friction rub with every movement. In a case reported by Gerhardt pulsation was discovered. Notable changes in size are often observed from time to time, and rapid decrease is especially prone to occur after an attack of diarrhœa or after severe hemorrhage. The subsidence of the symptoms and the decrease in the size of the organ occurring during intercurrent affections have already been referred to, but the fluctuations in size may at times take place without demonstrable cause.

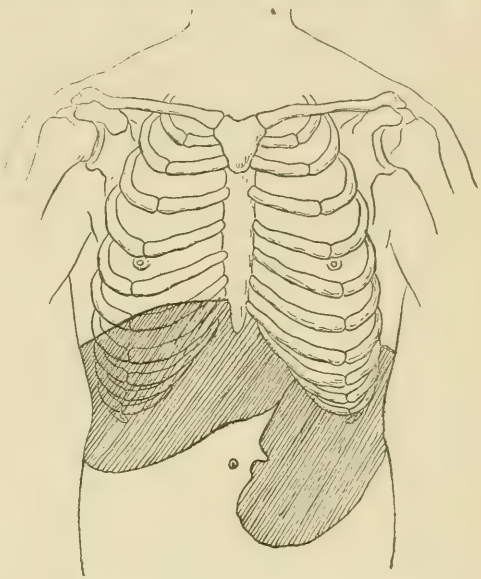

Fig. 42.—Diagram Showing Enlargement of Spleen and Liver in Leukæmia.

Symptoms denoting involvement of the bone marrow may become prominent. The most frequent condition is slight tenderness of the tibiæ, spine, or sternum, causing considerable sensitiveness to pressure or to blows. In other cases there is actual pain with exquisite tenderness in the regions mentioned. These symptoms may occur early in the disease and may lead to the recognition of the myelogenous nature of the case or they may pass unnoticed or develop late in the disease. The absence of pain by no means indicates absence of involvement of the marrow.

Gastrointestinal Symptoms.—Marked disturbances of the gastrointestinal functions are generally noted at some period of the disease. In acute cases the onset may follow an attack of pharyngitis or stomatitis, and small or large ulcers and hemorrhages in the mucous membrane of the mouth or pharynx may be noted. In other cases

diarrhœa is the first evidence of the disease; or this symptom may occur during the course of the affection, and may contribute to increasing weakness and a rapidly fatal issue.

In chronic cases the patient usually complains of loss of appetite, while the thirst may be considerably increased. Soreness of the mouth may cause discomfort and the lymphatic glands at the base of the tongue and the tonsils may be distinctly enlarged so that swallowing is difficult. Digestion is slow and regurgitation and eructations are frequent. Tenderness is often found upon pressure over the epigastrium and vomiting may prove distressing. Diarrhœa has been referred to. It is particularly marked in cases in which the solitary follicles and Peyer's patches are enlarged and ulcerated, as in the instances reported by Behier and subsequent writers. In these cases it is constant and severe, and leads to rapid emaciation. The stools are generally somewhat light colored and mucus is frequently present. Virchow found leucin and tyrosin abundant.

The Liver.—Enlargement of the liver is rarely absent in chronic cases and usually follows rather quickly after the enlargement of the spleen or of the lymphatic glands. There may be a certain amount of tenderness, but there is rarely pain. The lower border is generally plainly palpable and the edge is decidedly rounded. The enlargement of the spleen and of the liver together frequently leads to enormous distention of the abdomen. Ascites is a rare occurrence.

Nervous Symptoms.—The general condition of the patient varies greatly. Subjective symptoms may be entirely wanting, or, on the other hand, there may be a feeling of languor or of general depression sometimes leading to constant sadness, moroseness, or even melancholy. Headache is very frequently complained of and neuralgic symptoms are not unusual.

Severe nervous disturbances sometimes occur. Delirium or even a maniacal condition may result from the disturbed nutrition of the brain, while coma may be the terminal symptom. The implication of peripheral nerve trunks by leukæmic infiltration may lead to local palsies, as in the case of facial palsy recorded by May; and central disturbances may be due to the growth of leukæmic lymphadenomata within the skull, as in a case of Friedreich, or to cerebral hemorrhage.

In a case of Eisenlohr the symptoms were those of bulbar palsy, while in one of Bramwell in which the cerebral vessels were greatly distended the manifestations were those of intense mania.

Spinal symptoms are unusual. Priapism is a frequent condition, but is probably due to thrombosis in the cavernous bodies. The discovery of degenerations in the spinal cord, however, make

it likely that spinal symptoms may be found, if searched for, in all cases.

The temperature is frequently elevated from time to time, the fever having an irregular and indefinite character and rarely becoming marked. In acute cases the disease may manifest itself as an essentially febrile affection.

The Hemorrhagic Diathesis.—A tendency to hemorrhages is more or less marked in all cases. Nose-bleed has been noted by most observers, and this may at times be so serious as to require mechanical interference. The extraction of a tooth, the application of a leech, or trivial incisions upon the surface may cause fatal hemorrhages. Usually, however, the tendency is less marked and manifests itself merely in the occurrence of small petechial ecchymoses upon the skin, in localized hemorrhagic extravasation in the muscles or deeper parts, or in slight hemorrhages from the mouth, lungs, gastro-intestinal tract or urogenital system. Menorrhagia and metrorrhagia are not rarely met with in women, and in exceptional cases hemorrhages may occur in the brain or meninges.

Urogenital System.—The urine is usually pale in color and does not vary greatly from the normal quantity. The specific gravity may be increased. The quantity of uric acid and xanthin bodies is habitually increased, and a certain degree of relationship seems to exist between the quantity of these substances and the fluctuations in the number of leucocytes (Fraenkel). The relation of the nitrogen of uric acid to the total nitrogen of the urine was found by Bohland and Schurz to be 1 to 9, 1 to 12, and 1 to 24 as compared to the normal, 1 to 20. Peptonuria has been reported, but the presence of true peptone is very doubtful. Albuminuria is occasionally present and hæmaturia may occur in cases in which the hemorrhagic diathesis is marked.

The eyes not rarely present a certain amount of exophthalmus. This has been found to be due to lymphomatous growths within the orbit in certain cases, and large lymphatic masses have been found in the eyelids and about the orbits in a few instances. The lacrymal glands may be similarly involved. Liebreich first discovered the occurrence of changes in the retina, the so-called *retinitis leukæmica.* This is detected in one-third or one-fourth of all cases (Leber). The ophthalmoscope reveals marked pallor or an orange-yellow color of the retina; the veins are increased in size and may be strikingly tortuous, while their color is light red in comparison with that of normal veins. Occasionally a border of light color is seen outside the venous walls. The disc frequently presents a striking dimness, while the retina in general is of a dull color; and hemorrhages are

frequent, especially in the peripheral parts. Usually these are more or less light colored with a zone of darker red surrounding. Hemorrhages in the vitreous, lymphomatous nodules in the choroid or iris, and cataract have been reported. The vision is frequently not at all affected, though there are marked changes in the fundus of the eye. On the other hand, limited vision may be one of the first symptoms and the disease may be first recognized by the ophthalmologist. Distortion of the images or contraction of the field of vision are not unusual symptoms, and marked amaurosis may occur.

Disturbances of hearing are infrequent. Occasionally sudden deafness has been noted, as in the cases of Steinbrügge and Pepper, but more frequently ringing noises or metallic sounds are complained of. Vertigo is not unusual.

Menstrual disturbances are sometimes noted, as in other anæmic disorders, and occasionally menorrhagia becomes troublesome or dangerous. Pregnancy may occur and may go on to completion without serious mishap, as was illustrated in Cameron's case, in which three successive pregnancies were recorded. Excessive hemorrhage may, however, attend delivery.

Priapism has already been alluded to. Cases have been recorded in which it has lasted for periods of from a few days to ten weeks.

Acute Leukæmia.

A number of observations have been reported in which the clinical course of leukæmia was acute. Ebstein in his dissertation in 1889 collected seventeen instances of this character, and since that time additional cases have been reported so that the total number is now nearly forty. Undoubtedly some of these cases are of questionable character. In a number of them accurate examinations of the blood do not seem to have been made, while in others the distinction between leukæmia and leucocytosis due to various conditions was not established, while the possibility of acute symptoms developing in a latent or unsuspected chronic leukæmia has received little or no attention from authors reporting such cases. An elaborate consideration of the subject with the report of ten cases under his own observation was made in 1895 by Fraenkel; and Litten stated in the discussion that he had seen almost an equal number of similar cases, though he was disposed to question the propriety of calling cases acute leukæmia when the duration was four months, this being the limit set by Fraenkel.

The onset of these cases is usually more or less abrupt, though weakness and malaise may precede the more decided symptoms. Pain in the splenic region and in the limbs is sometimes noted.

The more characteristic symptoms, however, give to the clinical history of these cases the features of an acute and violent infection. The onset may be marked by a chill; and fever of irregular type, though of moderate severity, is usually present. The lymphatic glands become enlarged in most instances and the spleen as a rule presents some evidences of swelling. This was noted in all of the cases of Fraenkel, though it was absent in three of the instances recorded by Ebstein. Evidences of hemorrhagic diathesis are rarely entirely wanting and are frequently marked. Petechial hemorrhages under the skin and bleeding from the gums sometimes give the disease the features of hemorrhagic purpura or of severe scorbutus. Retinal hemorrhages were found in nine of Fraenkel's ten cases.

Hinterberger first called attention to the occurrence of ulcers in the mouth and other parts of the gastrointestinal tract. Such lesions are frequently observed. Examination of the blood shows marked leucocytosis with a preponderance of mononuclear cells. The hæmatological features are commonly those of lymphatic leukæmia, but myelocytes and nucleated red corpuscles have been discovered in some instances. Fraenkel called particular attention (*vide supra*) to certain moderately large leucocytes with pale nuclei which he believed to be derived from the lymphatic glands. In two cases under my observation similar forms were abundant, and I am disposed to accept the explanation given. In some measure the condition of the blood and in particular the abundance of small mononuclear cells may be due to hemorrhages.

The cases run a rapid course, varying from three days (Vehsemeyer) to ten or twelve days or more, a few to several weeks. The limit assigned by Fränkel is four months.

Complications.

Leukæmia is liable to a number of serious complications. Most of these have already been alluded to. Among those which are dangerous may be enumerated hemorrhages, either from the surface or into the interior, especially cerebral hemorrhages. Among sixty cases collected by Gowers six presented the last-named complication. Severe diarrhœa or other gastrointestinal disturbances are liable to occur in any case, but are more frequent in such as are characterized by leukæmic lesions of the gastrointestinal tract. Circulatory disturbances sometimes become marked, particularly œdema. Dropsy of the serous cavities is rare, but sometimes leads to a fatal issue. Acute endocarditis and acute inflammations of the other serous surfaces have been observed. Hemorrhages into the retina

and leukæmic retinitis are so frequent that they are scarcely to be ranked as complications. Reference has already been made to hemorrhages into the middle and internal ear, and to leukæmic infiltrations or exudations in the same structures. A fatal termination is occasionally due to pneumonia.

Diagnosis.

The diagnosis of leukæmia offers a number of difficulties. The onset of the disease may be so gradual and insidious that the cause of the patient's condition may not be suspected for a considerable time. The enlargement of the spleen, though it should always excite suspicion, may be taken for malarial hypertrophy or malignant disease. In children similar enlargement occurs in rickets and congenital syphilis, and the leukæmic nature of the disease may therefore be overlooked. Finally, it is practically impossible in many instances to distinguish by the clinical features alone between Hodgkin's disease and leukæmia.

The examination of the blood, therefore, is of prime importance. This examination, however, in itself may sometimes fail to establish the diagnosis, and it may be asserted that the condition of the blood alone and the occurrence of particular varieties of leucocytes will not serve to establish a positive diagnosis in all cases. It is necessary to consider the entire clinical history of the case, together with the condition of the blood. Puncture of the spleen has been practised in some cases for the removal of liquid to be examined microscopically. Charcot crystals have been detected in some of these instances, but the fact that death occurred in Westphal's case and that the data obtained in this way are comparatively insignificant makes the practice unjustifiable.

In the most frequent form of the disease, the lienomedullary, the excessive proportion of large mononuclear cells and in particular of those known as myelocytes, is of great importance. The occurrence of large numbers of nucleated red corpuscles, especially the large forms (megaloblasts), undoubtedly adds considerable weight to the evidence of myelogenic involvement. The proportion of eosinophilic cells, as has already been pointed out, may be greater or less than normal but furnishes no reliable points for diagnosis.

It is impossible to establish a diagnosis of simple myelogenous leukæmia, and it may be questioned whether any case of this kind has been observed. Those of Mosler, Fraenkel, and others have not sufficed to decide the question; and in any event clinical experience and pathological evidence point to the almost if not quite

invariable association of splenic involvement with disease of the marrow.

In cases of pure lymphatic leukæmia or in those in which the lymphatic glands are principally involved, the condition of the blood differs materially from that in the lienomedullary variety. The most striking characteristic is the unusual proportion of lymphocytes, these being of the ordinary variety or somewhat larger and with paler nuclei and almost wholly without granules. Myelocytes and nucleated red corpuscles may be present in small numbers but are inconspicuous.

The distinction between leucocytosis and leukæmia ordinarily presents little difficulty. The increased number of leucocytes is rarely as pronounced in simple leucocytosis as in leukæmia, and the older writers (Huss and others) distinguished the two conditions by the proportion of leucocytes to red corpuscles, holding that when the number of leucocytes increases beyond a proportion of 1 to 20 or 40 the disease should be characterized as leukæmia. Such a distinction is no longer entertained. The characteristic feature of leucocytosis, as we at the present time understand this condition, is increase in the number of leucocytes, of more or less transient nature, and usually affecting the polynuclear forms more than the mononuclear elements, though occasionally the various elements of the blood increase in equal ratio. In exceptional cases, as in post-hemorrhagic and terminal leucocytosis, the mononuclear forms predominate, but in such cases the smallest lymphocytes are particularly abundant. The high grade of anæmia, the extreme smallness of the lymphocytes, the presence of small nucleated red corpuscles, and the absence of organic lesions indicative of leukæmia distinguish such cases from lymphatic leukæmia. In leukæmia as distinguished from most forms of leucocytosis the preponderance of the mononuclear elements is always striking, the small forms predominating in lymphatic cases, the large forms in the lienomedullary type. The discovery of cells presenting karyokinetic figures is of some importance in making a diagnosis, though we cannot attribute the significance to this that was claimed for it by Müller. The study of the amœboid movements upon which Müller and Rieder have laid so much stress seems to afford little aid additional to that obtained by a differential count of the forms of leucocytes.

The diagnosis of leukæmia in early childhood is attended with special difficulties. Von Jaksch has described a group of cases marked by decided leucocytosis, enlargement of the spleen and liver, and other features resembling leukæmia, but tending to a favorable outcome. This condition, to which he has given the name "anæmia

infantum pseudoleukæmica," presents unusual difficulties for diagnosis. The differential diagnosis will be more fully considered in the section dealing with this affection.

At times in the course of leukæmia the improvement in the general symptoms, the subsidence of the leukæmic enlargements, and the disappearance of leucocytosis may be so complete that the diagnosis could scarcely be made should the case come under observation at such a time. In a short time a relapse may reestablish the former conditions. Osler and Thayer observed an instance of this kind and particularly directed attention to the difficulty of diagnosis during the remission. The persistence of a considerable percentage of myelocytes in the blood was the only suggestive feature remaining. Even this sign, however, may disappear, and the occurrence of small numbers of myelocytes is too uncertain to warrant a positive diagnosis, so that it is practically impossible to establish the existence of the disease under such conditions.

In cases in which the abdominal lymphatic glands and the spleen are mainly involved, there may be a certain resemblance to typhoid fever in the abdominal distention, splenic tumor, diarrhœa, and fever; but the irregularity of the latter and the atypical onset and course of the disease soon arouse suspicion, and the blood examination, which should always be made in cases of enlargement of the spleen if not in every patient, readily establishes the diagnosis.

Leukæmic disease of the skin may be unrecognized and may pass for ordinary prurigo, eczema, or other dermatosis. The prurigo associated with leukæmia differs from the ordinary form in its occurrence at any age instead of in the young, in the wide-spread character of the eruption, and in the fact that the glands are involved at the same time as the skin or even before the latter.

Cases of *acute leukæmia* are easily mistaken for purpura or scorbutus, and the diagnosis must rest upon the examination of the blood. Even in chronic cases, as in that of Sigel, the onset may be marked by hemorrhagic manifestations giving the appearance of purpura.

Acute leukæmia may occasion symptoms very like those of acute osteomyelitis (fever, bone pains, moderate enlargement of the spleen, leucocytosis). The distinction is usually made with ease. Acute leukæmia is characterized by a greater tendency to hemorrhages, with less pronounced bone pains and greater leucocytosis. Moreover, the character of the leucocytes is quite at variance from that seen in osteomyelitis, the latter disease being usually, though not always, marked by a preponderance of polymorphous elements.

Prognosis.

Leukæmia is almost invariably a fatal disease; instances of recovery have been recorded. The course is usually a chronic one and life may continue for five or even eight years after the disease has been recognized. The average duration, however, after the symptoms have become established is from one to three years. Intercurrent diseases may influence the disease unfavorably, but, on the other hand, the favorable effect of certain infections (typhoid fever, tuberculosis, and other diseases) is undoubted. Excessive hemorrhages, intractable diarrhœa, failing circulation, and fever may contribute to the increasing weakness of the patient, and death usually occurs from advancing anæmia and general adynamia. Rapid death may be due to pneumonia, hemorrhages, rupture of the spleen and peritonitis, rupture of the suprarenal capsules (Fleischer and Penzoldt), or cerebral hemorrhage.

As a rule the lymphatic form is more rapid than the lienomedullary type, but no invariable rule can be established.

Treatment.

Treatment offers but little prospect of permanent relief, though a notable amelioration of the symptoms may be secured and a prolongation of life with considerable temporary improvement may follow judicious care and medication. The patient should be placed under the best possible surroundings, all causes of grief and anxiety being removed, and, if possible, all attempt to continue his accustomed occupation should be given up. Removal to a different climate and especially to greater elevations sometimes influences the course favorably, while in other cases sea air is beneficial. The diet should be strictly regulated. Easily assimilable foods, especially carbohydrates and fats, should be given; and care should always be taken in the diet and medication that gastrointestinal disturbances are not excited, as diarrhœa is one of the most frequent causes of unfavorable progress of the disease.

Among the remedies advocated in the treatment of leukæmia arsenic alone has decided merit. This may be administered in the form of Fowler's solution, well diluted, and the dose should be increased as far as the gastrointestinal tolerance or the general condition will permit. It is sometimes advantageous to administer the remedy hypodermically. Fowler's solution diluted with an equal quantity of water may be used in such cases, or arsenate of sodium in

dilute solution may be even less irritating. Ordinarily from five to seven drops are well borne at first, but the quantity may be increased rapidly to twenty, thirty, or more drops three times daily. When improvement has begun to manifest itself in the decreased number of leucocytes and a subsidence of the splenic or lymphatic tumors, the dose of arsenic should be somewhat decreased. In all cases in which a beneficial effect is observed the remedy must be given without cessation except when toxic symptoms manifest themselves. Injection of arsenic into the spleen or glands (parenchymatous injection) has been practised, but offers no special advantages and is not free of danger.

Quinine has sometimes appeared to be of benefit in cases in which a malarial history has been obtained. Mosler recommended large and continuous doses of quinine, followed by oil of eucalyptus and piperine in such cases.

Local treatment directed to the spleen and to the lymphatic glands is sometimes of advantage in relieving the pain or discomfort, but has little value in controlling the disease. Cold douches or cold applications may be made directly over the splenic region and may be useful in the early stages, when the spleen is mainly congested. Injections of ergotin may be used in the same stages and have sometimes appeared to be of advantage. Faradization or galvanization over the splenic region has been practised; and actual galvano-puncture of the spleen has been performed by Salkowski and Leyden. It is doubtful, however, whether any of these measures have notable influence upon the course of the disease. The feeling of weight and pressure in the left hypochondrium may sometimes be satisfactorily controlled by the application of a well-fitting flannel binder.

Removal of the spleen or splenectomy has been performed in upwards of twenty cases, but with the exception of that reported by Franzolini, always with a fatal issue. Of the eighteen cases collected by Biziel rapid death occurred in sixteen from hemorrhage and in the other two from shock. In the successful case of Franzolini the proportion of leucocytes to red blood corpuscles was 1 to 74 and the diagnosis seems not altogether certain. Even should the operation be successfully performed it is doubtful whether any other than a temporary and ameliorating effect would follow, as in all probability the primary disease rarely resides in the spleen.

The transfusion of blood or the injection of defibrinated ox blood into the lower bowel was formerly recommended, but is of little value. It may exercise a temporary effect, but certainly has no permanent influence.

Inhalations of oxygen may sometimes prove useful. Kirnberger

asserts that he has seen recovery in a lad treated in this manner, while Sticker, Da Costa, and others have claimed excellent results. Kahler, Schultze, Stintzing, and others could find no effect at all. In one case under my own observation the effect was entirely negative.

The recent development of organotherapy has led to the employment of bone-marrow, splenic and other organic extracts in the treatment of leukæmia. In a few cases the administration of bone marrow has been reported to be useful. Theoretical considerations would scarcely lead us to expect favorable results from this method of treatment, and the whole question is entirely too unsettled to warrant an expression of opinion. The splenic extracts are apparently of no use at all. The general condition of the patient, and in particular the anæmia, makes the administration of tonics such as iron, cinchona, or nux vomica advisable. Iron has been frequently employed; in ordinary cases Blaud's pills or the tincture may be used, but the iodide seems to have somewhat greater effect in cachectic individuals.

The various symptoms call for special treatment. Disturbances of the stomach may sometimes require sedatives, such as bismuth or cocaine, or the bitters, such as gentian and nux vomica, when the appetite is poor and digestion sluggish. In cases in which constipation is marked the sulphate of berberin in doses of five to fifteen grains is a useful stomachic and laxative, but must not be pushed to the point of causing diarrhœa. Diarrhœa must always be treated promptly. Bismuth and creosote may be useful and intestinal lavage with astringent antiseptic solutions may be practised with advantage.

Hodgkin's Disease.

Synonyms.—Pseudoleukæmia (Cohnheim); Adénie (Trousseau); Anæmia seu cachexia lymphatica et lienalis; Lymphatic anæmia (Wilks); Lymphosarcom (Virchow); Malignes Lymphom (Billroth); Malignes aleukämisches Lymphadenom (Orth); Lympadénie (Ranvier); Desmoidcarcinom (Schulz); Lymphatic cachexia (Mursick); Cachexie sans leucémie (Bonfils); Adenoid disease (Southey); Anæmia splenica (Griesinger, Strümpell).

Definition.

Hodgkin's disease is a progressive and generally chronic anæmic disorder marked by enlargement of the lymphatic glands, of the spleen, or both, and with frequent involvement of the other lymphatic structures. An accurate and reliable definition of this disease cannot

be given at the present time. A study of the literature reveals a striking variability in the clinical course of the cases recorded, and undoubtedly very many different affections have been described under this name. The enlargement of the lymphatic glands and spleen and the anæmia which are characteristic of all cases are insufficient to establish and define a single form of disease, as these conditions are met with in a multitude of affections. Cases of tuberculosis, of inflammatory enlargement of the glands, of syphilis, of malignant tumors, and of other diseases figure among the conditions which have been considered as instances of Hodgkin's disease during life and even post mortem.

History.

Cases of enlargement of the lymphatic glands with more or less anæmia were observed and described by a number of the older authors, but the first accurate description of the disease was that of Hodgkin, who reported a series of cases from Guy's Hospital in 1832. Subsequently other physicians of the same hospital recorded cases and added to the more general recognition of the disease. Wilks in 1865 described a number of cases and spoke of the affection by the name of Hodgkin's disease. Cohnheim in 1857 studied the lesions and pointed out the similarity of the latter with those seen in leukæmia as well as the essential feature distinguishing it from leukæmia, the absence of leucocytosis, and applied the term pseudoleukæmia. The enlargement of the glands had previously been studied and described by Virchow, and the name lymphosarcoma was used by this author. A distinction between true sarcoma or lymphosarcoma and the enlargement of the glands characteristic of Hodgkin's disease was maintained by Billroth, who introduced the term malignant lymphoma to indicate the glandular enlargements of Hodgkin's disease.

Bonfils, Trousseau, and after him the French writers generally, dwelt more particularly upon the organic lesions and held that Hodgkin's disease and leukæmia are essentially similar diseases, applying the term *adénie* to indicate the common glandular affection. The existence of a form of splenic Hodgkin's disease was recognized by Wilks, Griesinger, Woillez, Müller, Landouzy, Strümpell, and more recently by Banti, Potain, Debove, and Bruhl. This form has been variously designated cachexia lienalis, anæmia splenica, splenomegalie primitive, and splenic anæmia. Fédé, Pepper, Wood, Cohnheim, Zenker, Hayem, and Luzet refer to lesions of the bone marrow, though in some of these cases pernicious anæmia was un-

doubtedly the disease under observation. Demange and Gilly described a form of the disease affecting the tonsils and the intestinal lymphoid tissue; while Trelat, Monod, and Terrillon maintain the occurrence of a testicular form, and dermal pseudo-leukæmia has been described by Gillot, Vidal, Brocq, Wagner, and Joseph.

Etiology.

The causes of pseudoleukæmia are extremely obscure, in large part on account of the difficulty of distinguishing the cases which properly belong in this category. As in the case of leukæmia, certain general diseases have been supposed to exercise an influence in determining the occurrence of Hodgkin's disease. Among these malaria, syphilis, scrofula, rickets, and chronic diarrhœa are usually specified, but it is difficult to determine with what frequency these influences are operative and to what degree the supposed relationship is dependent upon incorrect diagnoses.

Surrounding conditions seem to exercise a certain influence and the disease is probably more frequent in the lower classes. Chronic alcoholism has been regarded as a contributing cause.

The disease affects males more frequently than females and is more common in the young than in the old. According to Gowers it is most frequent between the twentieth and thirtieth years and between the fiftieth and sixtieth, while Osler states that sixty per cent. of the cases occur in persons under forty years. It is not unusual in early infancy and childhood, though the diagnosis is particularly difficult in children, and other conditions are frequently called Hodgkin's disease.

It is met with in all parts of the world and probably with about equal frequency in different places. Eichhorst states that while he found leukæmia more frequently in Königsberg and in Göttingen than in Zurich, the reverse was true of pseudoleukæmia. The affection is not confined to the human race but has been described in animals, notably horses.

Sometimes Hodgkin's disease has been found to follow certain local diseases, such as otorrhœa and coryza (Trousseau), quinsy (Ponfick), and ulcerative pharyngitis (Chvostek). I have myself observed one case in which primary enlargement of the glands of the neck and secondary involvement of the entire lymphatic apparatus with cachexia followed caries of the teeth and necrosis of the lower jaw.

Infection.—The clinical course of the disease and in particular the occurrence of fever of irregular but more or less recurring type, and

the peculiarly rapid and malignant course of some of the acute cases, suggest the likelihood of infection. The same thought is brought to the mind by the pathological anatomy, as Virchow first pointed out, and especially by the metastatic character of some of the lesions. Finally a number of observers have found definite micro-organisms. Majocci and Piccini found mixed infection with bacilli and streptococci, Klein demonstrated the presence of micrococci, and Mafucci found streptococci in the enlarged glands. Roux and Lannois discovered the Staphylococcus pyogenes aureus and were able to produce glandular enlargements in animals by injection of cultures from the blood and glands of their patient. Delbet isolated a bacillus from the spleen and, injecting this into dogs, produced glandular enlargements.

A complete review of the literature by Verdelli showed that there have been recorded some twenty-nine cases in which positive results have been obtained from the bacteriological studies. Against these, however, may be urged the fact that Westphal was unable to find micro-organisms of any kind, and the more important objection that the mere discovery of micro-organisms in no way proves the infectious nature of a disease. Recent studies in bacteriology, such as those of Flexner and others, show the great frequency of terminal infection in various diseases, and I can substantiate this from my own limited experience in twenty-five or more cases. In each of these some form of bacteria was found in the blood, spleen, or other tissues. It is altogether likely, therefore, that the micro-organisms found in cases of pseudoleukæmia have been largely of the same significance. The fact that certain investigators were able to demonstrate glandular enlargements after injection of their cultures is no more surprising than the discovery of the micro-organisms themselves. These enlargements occur in a great variety of infections and are of no particular significance. Considerable interest attaches in this connection to the report of Gabbi and Barbacci, who found the bacillus coli communis in the glands. In this case there was almost certainly an accidental infection.

A number of investigators have discovered tubercle bacilli. This is undoubtedly of greater significance, as accidental infection with this micro-organism is decidedly less likely to occur than with the ordinary cocci. Askanazy (1888) was the first to demonstrate tubercle bacilli in the glands. Subsequently cases have been recorded by Wetzoldt, Brentano and Tangl, Weishaupt and Conbemale. It is not unlikely that general lymphatic tuberculosis may present clinical features indistinguishable from pseudoleukæmia, and it may be that the diseased gland is a *locus minoris resistentiæ* in which the tubercle

bacillus may secondarily find a favorable soil. It is quite certain, however, that this bacillus is not concerned in the great majority of cases, and the inclusion of the cases of primary lymphatic tuberculosis, if such these cases be, in the group of Hodgkin's disease is an evidence of the indefiniteness of the limitations thus far established.

Pseudoleukæmia and leukæmia are undoubtedly closely allied diseases. The similarity in the pathological anatomy was first recognized by Cohnheim after Virchow had described the glandular lesions of leukæmia; and Bonfils and Trousseau with subsequent French writers, used the term *adénie* to indicate the essential unity of the morbid changes in the two diseases. The most striking evidence, however, of the close relationship of these affections is the occurrence of leukæmia as a terminal condition following Hodgkin's disease. Cohnheim and other German writers have therefore designated the latter condition as the aleukæmic forerunner (*Vorstadium*) of leukæmia. Among those who have recorded instances of transformation of pseudoleukæmia into leukæmia are Biermer, Olivier, Vidal, Laache, Crocq, v. Limbeck, Fleischer and Penzoldt, Rendu, Mosler, Senator, and Westphal. In some of these cases terminal leukocytosis may have been mistaken for leukæmia, but it is undoubtedly true that an actual transformation may occur. The infrequency of this occurrence may be due to the fact that termination of the disease by intercurrent affections takes place before the transformation has had time to manifest itself. It is more likely, however, that many cases are of such nature that a conversion into leukæmia will not occur under any circumstances. Unfortunately, there is nothing to indicate the nature of the underlying condition which leads to this distinction.

Pathological Anatomy.

In general the anatomical features of Hodgkin's disease resemble those of leukæmia so closely that it may be impossible to distinguish between the two affections. The lymphatic glands are primarily involved in the majority of instances, although occasionally primary implication of the spleen occurs and possibly the bone marrow may be the initial seat in other instances, though this has not yet been definitely determined. Dermal leukæmia and gastrointestinal forms may also be distinguished. Secondary infiltrations or nodular lymphomata are observed in the liver, the kidneys, the mucous membranes, the heart, the lungs, and other structures.

The Lymphatic Glands.—The lymph glands are usually affected in groups. A single gland may be first enlarged or the entire group

may be involved simultaneously. Eventually bunches or chains of much enlarged glands are formed and may constitute tumors of considerable size, projecting upon the surface in the case of superficial groups or causing pressure symptoms or palpable masses in the case of the internal glands. The pathologists have distinguished two forms, the soft and hard but there is no essential, difference between the two and in reality they represent only stages in the same affection. In the earlier periods the glands are soft and on microscopic examination are found to consist of masses of round cells embedded in the lymphatic tissue. In the later stages proliferative changes affecting the connective-tissue stroma and the vascular walls become more and more marked, and in proportion to the degree of this change the consistence of the glands increases until in some instances they become stony hard. In typical examples the process does not tend to spread beyond the limits of the gland, but sometimes the capsule is penetrated and periglandular proliferation ensues. Billroth sought to distinguish between lymphosarcoma and Hodgkin's disease or malignant lymphoma, as he termed it, according as the shape of the gland and the capsule remained preserved or proliferation occurred externally. This distinction, however, cannot well be maintained. In the great majority of cases the glandular disease remains limited within the capsule, but in other cases (cases in no way distinguishable from the former) periglandular involvement does occur. Degenerative changes may ensue from pressure or from secondary infection. These small areas of necrosis are not unusual, and complete softening or caseation is sometimes seen; but actual suppuration dependent upon secondary infection with micrococci is rare. Amyloid degeneration of the blood-vessels or of the connective tissues is occasionally witnessed. The tumors may have a greenish discoloration, corresponding to the form of sarcoma termed chloroma.

Enlargement of the spleen is very frequent, having been present in seventy-five per cent. of Gowers' series of cases. The enlargement may be uniform or there may be distinct nodular lymphomata, the latter occurring in fifty-six per cent. of the same series. The organ is primarily soft, but soon increases in density and in the end may become quite hard. On section the color is dark red with scattered areas of light color or distinct nodules composed of round cells embedded in a lymphadenoid network. The size is rarely as great as in cases of leukæmia, but instances in which the organ has practically filled the left side of the abdomen have been recorded and the weight may be from five to ten or more times the normal. The changes in the bone marrow are practically the same as those met with in leukæmia, though they are rarely as pronounced. Enlargement of

the thymus gland and involvement of the thyroid body have been frequently reported.

Involvement of the liver and of the kidneys is met with as in leukæmia, though the liver is rarely as much enlarged and the lymphomatous infiltration of either of these structures is not so pronounced as in that disease. Amyloid degeneration may occur in the liver and kidneys as well as in the intestinal tract and may influence the clinical course of the disease.

Lymphomatous nodules in the gastrointestinal tract have been frequently described. In many cases the tonsils are enlarged simultaneously with the swelling of the superficial glands; while in rarer instances nodules may be found in the mucosa of the stomach or intestines. It is not unlikely that cases of primary gastrointestinal pseudoleukæmia may occur, though such instances are rare. The literature contains a few instances of primary lymphoma of the stomach in which the tumor reached considerable size.

The lungs may be secondarily involved after the enlargement of the bronchial glands, or in consequence of extension of nodules from the bronchial tubes. Usually the changes are slight, though occasionally the infiltration is decided.

Dermal pseudoleukæmia presents itself in the form of more or less diffuse or nodular elevations in the skin which tend to ulcerate upon the surface. This condition, described by Alibert under the name of mycosis fungoides, has subsequently been particularly studied in its relations with Hodgkin's disease by Vidal, Brocq, and others. Wagner and Joseph reported cases in which the lesions were closely allied with prurigo, though differing in some particulars, and Recklinghausen includes the indefinite condition known as lichen ruber acuminatus as probably a form of leukæmia or pseudoleukæmia of the skin. The histological features of all of these conditions are essentially those met with in the lymphatic structures; and cachexia is prone to occur in all of them. Nevertheless it is questionable whether the classification of these conditions as pseudoleukæmia cutis is justifiable.

Occasional involvement of other portions of the body, such as the heart, the serous surface, the testicles and other genital organs, the nervous system, or the suprarenal capsules has been observed.

The Blood.—The blood of pseudoleukæmia is distinguished by the absence rather than the presence of alterations from the normal. In most cases the number of red corpuscles is decreased, though this decrease is frequently slight. In severe cases reduction to 2,000,000 or even 1,000,000 may occur, and the individual red corpuscles may show alterations in their shape and size such as occur in other forms

of severe anæmia. The white corpuscles are usually about normal in number, though they may be a little increased or a little decreased. Intercurrent conditions may induce a temporary leucocytosis of more or less pronounced character in certain instances, and the number of leucocytes may be permanently increased, though never greatly. The leucocytes do not differ in character from those seen in the normal blood. The relative proportion of the different forms is preserved in most instances, but occasionally a predominance of small mononuclear forms has been alluded to, this condition doubtless standing in some relation with the lymphatic disease. In the late stages when secondary infections have developed, the polynuclear elements may become predominating.

Symptoms.

The onset of pseudoleukæmia is usually marked by a more or less gradual enlargement of the cervical lymphatic glands. Exceptionally the disease may begin with a similar enlargement of other groups. The glands first involved increase to a considerable size, and the process then extends to the same group on the other side of the body or to other groups. Exceptionally an acute onset and a rapid progress are observed. In such cases the earliest symptoms may be feverishness and a feeling of general illness or purpura and other hemorrhagic manifestations. Sometimes the disease begins with angina and is followed by enlargement of the tonsils and subsequently of other lymphatic structures. In the splenic form of the disease the first manifestation may be general pallor and weakness or a feeling of weight and heaviness in the left hypochondriac region, while in other cases epistaxis, purpura, or similar conditions mark the inception of the disease as in acute cases.

Lymphatic Glands.—The enlarged lymphatic glands form the most striking feature among the objective manifestations. The cervical and submaxillary glands grow progressively larger and project from the surface as large clusters or bunches or in the form of chains extending from the angle of the jaw to the clavicle. Usually there is no pain or even tenderness, but exceptionally considerable tenderness is complained of and radiating neuralgic pain may extend along the occipital region or downwards into the arms when nerve trunks are compressed. The skin over the affected glands usually presents no distinct alteration. Occasionally a certain amount of periglandular involvement or inflammation may lead to infiltration and redness of the skin as well as to firm attachment between the skin and the glands. The latter, however, is quite exceptional. The glands in the

earlier stages are soft and sometimes may be almost fluctuating; in the later stages they become progressively harder, though sometimes secondary necrosis leads to considerable softness at this period. Marked variation may be noted from time to time in the size of the glands, so that while strikingly rapid increase in size is occasionally observed, at other times the swellings as rapidly subside. This is true of the external glands and also of those in the interior, and in the latter case corresponding increase and decrease of the pressure phenomena ensue. Suppurative softening of the glands is excessively rare.

Next to the cervical glands, the axillary and inguinal groups are involved with about equal frequency. In this way large bunches may form beneath the arms, and may cause considerable discomfort on account of their position and from the pressure exerted upon important structures in the axilla. The enlargements in the groin may project as decided tumors.

Involvement of the internal glandular groups is less frequently noted, though cases of Hodgkin's disease beginning primarily in the tracheal and peribronchial groups, in those of the anterior mediastinum, in the mesenteric, periportal, retroperitoneal, and even in the pelvic lymphatic nodes are occasionally observed. In these cases the nature of the disease may be extremely obscure and its manifestations may be largely mechanical, due to pressure.

The Spleen.—A certain amount of splenic hypertrophy may be observed in the great majority of the cases, while in a small number the splenic hypertrophy reaches considerable proportions. The increase in the size of the spleen may occur gradually and progressively, or, on the other hand, may take place very rapidly. In such instances pain is often a prominent symptom, while in other cases an indistinct feeling of heaviness or dragging upon the left side is complained of. Fluctuations in the size of the spleen are met with, as in that of the lymphatic glands, and hemorrhages, diarrhœa, or similar conditions may be found to exercise a potent influence in this direction. In cases of moderate enlargement the edge of the spleen may be felt just below the border of the left ribs, while in more decided cases the lower half of the organ may be grasped in the hand as the patient lies upon the back with the thighs flexed upon the body. In cases of the most pronounced character the lower end of the organ may extend to the brim of the pelvis, and the anterior border may lie in the median line.

Splenic hypertrophy may be unassociated with changes in the lymphatic glands or other structures. Such cases constitute the splenic anæmia of Griesinger and Strümpell, or the splenomegalie

primitive of Debove and Bruhl. More commonly the splenic enlargement is followed by some involvement of the lymphatic glands, and the latter may eventually become the more conspicuous feature of the disease.

Capsular peritonitis may occasion attachments of the spleen to the surrounding organs, giving rise to localized pain and tenderness and sometimes to a friction rub which may be plainly palpable.

Conspicuous involvement of the spleen is more common in Hodgkin's disease when it occurs in children, and Carderelli, v. Jaksch, and others have described special forms of the disease occurring in early life. The nature of these cases, however, must be more definitely established. Some of the instances reported are certainly in no sense related to true Hodgkin's disease.

There may be symptoms pointing to involvement of the bone marrow, but such are rare. Among these pain and tenderness along the limbs and particularly beneath the sternum are sometimes noted, but practically never become severe or urgent.

External Appearances.—The general appearance of the patient in Hodgkin's disease may be decidedly striking. In case the superficial glandular tumors are large, the projecting bunches of cervical, inguinal, or axillary glands may give a most decided picture to the disease; but when such enlargements are not prominent the marked pallor or the somewhat sallow hue of the patient's skin may attract attention. Extreme pallor is unusual, though at times it is noted, especially in cases marked by hemorrhage and in pseudoleukæmia occurring in early life. Pigmentation of the skin has been observed by a few writers (Marvin, Wright, Ferreol, and Eichhorst). It may affect exposed portions of the body or may be quite generally distributed in a diffuse or in a patchy fashion. In some of the cases in which it has been seen enlargement of the spleen or of the abdominal glands was a conspicuous feature, and pressure upon the suprarenal capsules or upon the solar plexus might with considerable propriety be looked upon as the cause of the pigmentation. Smaller areas of pigmentation are not unusual and owe their presence to deposition of pigment after ecchymotic hemorrhages.

Various forms of local lesions have been observed in the skin, the most characteristic and important of which are ecchymoses. Small petechial hemorrhages not rarely appear from time to time, and large hemorrhagic suffusions may cover a considerable portion of the extremities and may involve the skin of the trunk as well. In such cases the clinical picture is that of purpura hæmorrhagica, and in many instances in which the post-mortem examination has determined lymphatic lesions such as occur in Hodgkin's disease, the

clinical manifestations have been those of morbus Werlhofii. The hemorrhages may appear with considerable regularity or may occur paroxysmally. In acute cases the onset of the disease is not infrequently marked by manifestations of this character. Other lesions of the skin, such as erythema and pemphigus, have been observed in certain instances.

Besides these dermal conditions in association with ordinary Hodgkin's disease there are the cases in which the involvement of the skin is the primary and most striking feature of the disease from first to last. In this case there are nodular elevations presenting a more or less reddish color and varying in size from a hempseed to considerable patches. Ulceration may occur upon the surface and the neighboring lymphatic glands become secondarily enlarged, while at the same time the patient's general health suffers considerably and marked anæmia is gradually developed. In instances of this kind the resemblance to prurigo is extremely close and the diagnosis is sometimes made with great difficulty, if indeed a distinction is at all possible. In other instances the lesions of the skin are those of mycosis fungoides.

In most instances the skin is dry and not rarely it is harsh. Sometimes, however, sweating is a marked feature, particularly when paroxysms of fever occur, and drenching, colliquative sweats may occur at night, suggesting that the condition is tuberculous. This resemblance is still further augmented by the occurrence of irregular fever.

Subcutaneous œdema may occur in the later stages in consequence of increasing anæmia and circulatory failure; and a certain amount of fugacious swelling about the malleoli and under the eyes is not rarely present in the earlier periods of the disease. Localized œdema may be dependent upon the pressure of the enlarged glands, as in cases of dropsical swelling of the arms, neck, and upper part of the thorax, due to involvement of the axillary, cervical, and intrathoracic glands. Serous effusions in the pleuræ, pericardium, and peritoneum may result from similar causes.

Evidences of a general hemorrhagic diathesis may be striking. Epistaxis is one of the commonest conditions and may prove serious. Hemorrhages from the stomach, from the respiratory tract, or from the urogenital system are frequently noted, while melæna has been particularly observed in children.

Subjective Symptoms.—The subjective symptoms are sometimes pronounced and at other times are much less prominent than the objective features of the disease. As in leukæmia and in other forms of anæmia, there is increasing weakness dependent upon the amount of

deterioration of the blood; the patient complains of languor, of palpitations, of loss of appetite, of digestive disturbances, and of dyspnœa upon slight exertion; while ringing in the ears, vertigo, disturbances of vision, and headaches may be more or less pronounced in accordance with the condition of the blood and of the circulation.

Examination of the heart may reveal hæmic murmurs at the base and sometimes at the apex, while venous and arterial phenomena are present as in other anæmias, although they are not usually pronounced.

Gastrointestinal Symptoms.—The gastrointestinal symptoms may be simply due to anæmia or may be still further influenced by the occurrence of specific lesions in the mucous membranes. Stomatitis and pharyngitis may be among the early manifestations in certain cases and have indeed seemed to be the primary cause of the disease in some instances. At other times they are secondary to the general manifestations. The lymphatic structures at the root of the tongue, the tonsils, and the pharyngeal lymphadenoid tissues may be increased in size, and erosion or actual ulcerations may occur. These symptoms are particularly prone to occur in acute cases. Pseudoleukæmic tumors of the stomach may be of such size as to be detected by physical examination, but marked gastric symptoms are infrequent. The bowels are usually constipated; but in cases in which specific lesions of the intestine have developed, attacks of diarrhœa are not unusual, this being particularly the case in the rare instances in which the intestinal nodules have undergone ulceration. Obstinate diarrhœa may also be due to amyloid degeneration.

Enlargement of the liver may occur early and may progress as in leukæmia. A certain amount of tenderness or weight in the right hypochondriac region is not unusual, but actual pain is rare.

The *temperature* shows striking peculiarities. From time to time paroxysms of fever of irregular type and of variable duration take place, alternating with apyretic intervals. The paroxysms may coincide with involvement of new groups of glands or may be entirely independent of such conditions. In other cases the fever is more constant and more uniform, and may suggest typhoid fever in cases in which the internal rather than the superficial glands are involved. Finally in some instances decided irregularity of the temperature may occur and may be associated with drenching sweats, suggesting tuberculosis. The irregular recurring type of fever was first noted by Pel, and later Ebstein suggested the title chronic relapsing fever in describing a case in which he believed the disease was of a specific and peculiar character. The occurrence of fever was also alluded to

by Bennett in the description of some of his cases. Recent studies show this to be one of the distinctive symptoms.

The *urine* presents no marked peculiarities. The quantity is usually about normal, though it may be increased or decreased; it is generally light-colored, and on chemical examination the quantity of uric acid is found to be about normal or even decreased. The other constituents of the urine are likewise normal. Occasionally albuminuria occurs.

Complications.

Various complications have been referred to in the description of the symptoms, but those due to pressure or to secondary infections remain to be described. The enlarged glands not rarely press upon nerve trunks and thus localized palsies or sensory manifestations may be produced. One of the most frequent results of this character is paralysis due to pressure upon the recurrent laryngeal nerve. In a case of Neusser's alluded to by Ortner there were distinct gastric crises ascribed to involvement of the sensory branches of the spinal nerves, while in a still more remarkable case of Ross and Osler there were lancinating pains and œdema of the feet, followed by complete paraplegia, all of these symptoms being due to pressure of a mass of glands upon the spinal cord.

Enlargement of the intra-abdominal glands may lead to jaundice by compression of the biliary duct or sometimes to ascites. Amyloid disease may occur in the liver, the kidneys, and the intestines, and may occasion great enlargement of the liver, increasing œdema, albuminuria, obstinate diarrhœa, and great cachexia.

Pulmonary complications are not infrequent. Pressure upon the trachea or bronchi may occasion serious disturbances of respiration, manifesting themselves in the form of extreme dyspnœa, stridor, or evidences of imperfect aëration of one or both lungs. Secondarily partial collapse or inflammatory lesions of the lungs may ensue; and pneumonia is not infrequently developed before the fatal issue of the case. Phthisis has been referred to by Claus as an occasional complication.

The transformation of Hodgkin's disease into leukæmia has been frequently observed. Doubtless some of these cases are instances of terminal leucocytosis, but the conversion into actual leukæmia certainly does occur. The opinion has been entertained that Hodgkin's disease represents a primary and aleukæmic stage of the affection, which eventually manifests its true characters as a fully developed leukæmia. There is much to be said in favor of such a view, but the relations of the two conditions have not as yet been determined.

There are certainly, however, other factors than the mere question of time which lead to the development of the leukæmic condition of blood in certain instances. Some cases show no tendency to become leukæmic despite their continuance for unusual lengths of time.

Course and Prognosis.

The course of the disease is usually subacute or chronic. In most instances it is more rapid in its development and course than leukæmia, though sometimes instances are observed in which the affection has lasted for a number of years. Marked variations may be noted from time to time, and sometimes the process seems to become arrested at a certain stage, and such arrests may be enduring. Usually, however, the fluctuations are transitory, and in the majority of instances the entire course of the disease is from one to two years. Acute and even fulminating cases have been recorded. Ebstein called attention to such in his dissertation in 1889, and other cases have since been recorded. The duration in these may be from a few days to several weeks, but it must be confessed that the diagnosis in such instances is frequently open to not a little suspicion. Complications render the course of the disease more rapid and cause marked fluctuations in the patient's condition. Thus attacks of diarrhœa, of hemorrhage or of high fever may occasion rapid increase in the anæmia and other untoward conditions. Death usually occurs from gradual increase in the general weakness and cachexia, the evidences of anæmia becoming more and more pronounced. Finally inflammatory conditions of the lungs, general anasarca or internal effusions, and heart failure may arise and determine the fatal result. Undoubtedly terminal infection is very frequent and the microorganisms (streptococci, staphylococci, bacilli) reported by various authors have been evidences rather of such terminal infection than indications of the etiological factors in the disease.

The prognosis, though nearly always absolutely unfavorable, is not in every instance hopeless. Cases of arrest of the disease have been recorded and entire subsidence under treatment is not impossible.

Diagnosis.

In cases of chronic Hodgkin's disease the diagnosis presents but little difficulty. The enlarged lymphatic glands, the swelling of the spleen, and the growing cachexia, together with the examination of the blood showing absence of leucocytosis, constitute a group of manifestations scarcely mistakable. The diagnosis, however, is extremely difficult in atypical and ill-developed cases.

Other diseases manifesting themselves by enlargement of the glands may be mistaken for Hodgkin's disease. Among these syphilis, tuberculosis, and malignant tumors must be considered. Syphilitic enlargement of the glands in ordinary cases is recognized without great difficulty by the associated dermal manifestations, the history of the case, the rather acute and benign course of the condition, and the fact that the glandular enlargements are moderate in their size and develop simultaneously in all parts of the body. The greatest difficulty occurs in the cases of tertiary gummatous enlargement of the glands (*lymphoma seu bubo gummosa seu tertiaris* of Lustgarten). In these cases the glandular involvement is usually localized and may reach considerable size. The history of the case, however, aids the diagnosis, and attachment to the skin and a tendency to ulceration or to softening distinguish the syphilitic disease from Hodgkin's disease.

Scrofulous or tuberculous lymphatic glands are usually distinguished by the fact that they occur more commonly in the young and remain circumscribed to a single group or to a small area. The submaxillary and the cervical glands are most frequently involved, and softening is as common in tuberculosis as it is rare in Hodgkin's disease. Ocasionally universal disease of the lymphatic glands may occur, and in such cases it is practically impossible to establish a diagnosis during life. Even in such instances, however, the tendency to softening and suppuration is of some assistance. Coincident tuberculous disease of other parts or the discovery of a primary focus of infection, such as tuberculous laryngitis or pharyngeal or tonsillar ulceration, may establish the diagnosis.

In a number of cases recorded in the literature the tuberculous nature of the glandular disease was unsuspected until after death and when injection of parts of the glands had been practised upon animals. Some have maintained that Hodgkin's disease is merely a general lymphatic tuberculosis; but such a view is certainly unwarranted.

Malignant tumors of the lymphatic glands when they are secondary offer but little difficulty in diagnosis if the primary growth is discoverable. Primary neoplasms (lymphosarcoma) cannot so easily be distinguished. Indeed, the limitations between this affection and Hodgkin's disease have not been established. Billroth and others after him have insisted upon the point that lymphosarcoma tends to spread locally from the glands involved to the surrounding structures rather than to other groups of glands. In the case of the superficial glands periglandular involvement and attachment of the skin are thus established, and the growth is characterized by a degree of irregularity

unusual in Hodgkin's disease. This distinction, however, cannot be admitted in all cases. There are undoubted cases of Hodgkin's disease with marked irregularity of outline of the glandular masses; and cases of lymphosarcoma in which the reverse is true. Leucocytosis with abundant lymphocytes would point somewhat in favor of lymphosarcoma.

Enlargement of the spleen from chronic malaria, rickets, congenital syphilis, amyloid disease, or congestion may occasion a resemblance to Hodgkin's disease of splenic type.

The diagnosis is to be made in such instances by exclusion. The fact that splenic anæmia or Hodgkin's disease is usually attended with some lymphatic enlargement may be of considerable assistance in the diagnosis, while the course of the affection, the occurrence of hemorrhagic manifestations, and the absence of indications pointing to other diseases establish the diagnosis in most instances. The greatest difficulty occurs in children in whom chronic enlargement of the spleen with cachexia is so frequent and of such varying significance (see *Anœmia Infantum Pseudoleukæmica*).

In acute or subacute cases of Hodgkin's disease the manifestations may suggest various infections. Instances marked by a continuous febrile course may be distinguished from typhoid fever with some difficulty on account of the enlargement of the spleen, the general weakness, and the abdominal distention. Particularly is this true of cases of Hodgkin's disease affecting the abdominal glands from the first or mainly. In time, of course, the diagnosis is easily established, and in most instances in which the history from the beginning is obtainable little difficulty exists.

In very acute cases the manifestations may be those of purpura hæmorrhagica, the real nature of which can only be suspected when distinct evidences of involvement of the lymphatic glands or spleen are obtained. Stress has sometimes been laid upon hemorrhagic manifestations as indicative of leukæmia or pseudoleukæmia, but at the present time these symptoms are recognized to be of little value in diagnosis, occurring as they do in a multitude of affections.

Pseudoleukæmia cutis may be distinguished from prurigo by the fact that the latter occurs more frequently in childhood and is more strikingly confined to the extensor surface of the limbs. It occurs coincidently with glandular disease or subsequent to the latter, while prurigo may be unassociated with glandular enlargement or precedes the swelling of the glands.

The differential diagnosis between Hodgkin's disease and leukæmia rests entirely upon the examination of the blood (see Leukæmia).

Treatment.

Hygienic measures should never be neglected in this disease, and local treatment should be directed to the conditions which may stand in etiological relation with the development of the lymphatic disease. The patient should be placed amid the most favorable surroundings, and a change of air and general scene may be advantageous. The diet should be nutritious and easily digested.

Among the remedies which have been found useful in this disease arsenic deserves most confidence and should be administered in increasing doses as soon as the infection is recognized. It is given in the form of Fowler's solution after meals, the doses being increased from five to ten, or even twenty or thirty drops, care being taken that at the first evidence of toxic action the quantity administered is reduced or the remedy is discontinued entirely for a time. Sometimes improvement is noted from the first; in other cases no change is obvious until the fullest therapeutic effects of the remedy have begun to manifest themselves. Injection of arsenic subcutaneously may be advantageous when the stomach is irritated, but the direct injection of arsenic into the glands or even into the spleen cannot be recommended. Iron, phosphorus, cod-liver oil, strychnine, and other tonic remedies possess certain advantages, though they are not to be used to the exclusion of arsenic, but only as adjuvants.

Local treatment has frequently been employed. Applications of strong ointments of iodine or of the tincture of iodine are certainly useful in cases in which there is irritation. It is doubtful, however, whether they have any effect in the way of causing absorption of the glandular hyperplasia. The same may be said of the internal use of iodine or the iodides, and of the local application of mercurial preparations. Galvanism of the lymphatic tumors has been recommended, and Meyer claims to have obtained excellent results from strong faradic currents.

Surgical treatment may possibly offer some hope of benefit if employed early and the removal of the first glandular enlargements may possibly arrest the disease. Evidence, however, is still wanting upon this point. The removal of the spleen, though it has been practised with success in a number of cases looked upon as Hodgkin's disease, is a serious operation, and offers too little chance of permanent improvement to justify the risks. Moreover, the splenic enlargement is so rarely primary that the same happy effect cannot be expected of this operation that has sometimes appeared to attend removal of primary glandular enlargements.

Anæmia Infantum Pseudoleukæmica.

Definition.

Von Jaksch in 1889 and subsequently described a form of anæmia occurring in children and distinguished by the following features: "There is often marked swelling of the spleen, the liver, and the glands, with continuous and decided leucocytosis. The relation of the white blood corpuscles to the red may be 1 to 20, 1 to 17, or 1 to 12, but despite these features there is no evidence of leukæmia at the post-mortem examination."

A similar affection had been recognized by Italian writers and had been styled *anemia splenica infettiva dei bambini.* Subsequently Hayem, Baginsky, Somma, Luzet, Loos, Alt and Weiss, and other writers recorded cases or contributed to the study of the disease. Notwithstanding the opinion of some of these authorities no definite characters can be ascribed to this affection, and it must be recognized rather as a clinical picture which may occur in a variety of affections, than as a distinct entity. In no sense is this condition allied to leukæmia or pseudoleukæmia, since the characteristic lesions of the lymphatic apparatus are entirely wanting—the enlargement of the spleen, of the liver, and of the lymphatic glands being of different sorts.

Etiology.

The condition occurs most commonly in children under the age of four, and especially between the seventh and the twelfth months. Luzet held that it does not occur after the age of two years. Of 20 cases collected by Monti and Berggrün all were under the age of four and 12 occurred before the age of twelve months. No special influence can be ascribed to sex, though Hock and Schlesinger believed it to be more common in male children. Monti and Berggrün found 11 girls and 5 boys among the 16 cases in which the sex was noted. Of the conditions which are closely associated with this form of anæmia rickets is most important, 16 of 18 cases collected by Fischl showing evidences of this condition, and 16 of the 20 cases collected by Monti and Berggrün presenting a similar history. Next to rickets, hereditary syphilis is of importance, and in other cases gastrointestinal disturbances, particularly chronic diarrhœa, seem to play a part.

It is somewhat difficult to estimate the frequency of this affection from the meagre knowledge thus far acquired. Luzet ranks it as

exceedingly rare, while Hock and Schlesinger found on the average 1 case in 1,000 or 1,500 children. Monti and Berggrün saw 5 cases among 4,851 children coming under their observation in eight months.

The disease occurs in all parts of the world, but whether with equal frequency or not cannot as yet be determined. Rotch refers to four cases that have come under his observation in Boston, and a recent case occurred in my ward at the Children's Hospital of Philadelphia

Pathological Anatomy.

The most conspicuous feature of the disease is the splenic enlargement which is regarded as one of the essential conditions. Sometimes this is slight, at other times the entire left side of the abdomen is filled by the splenic tumor. The organ is hard, and on section is dark red in color. Not rarely the surface is somewhat roughened, and evidences of perisplenitis are observed (Luzet). The histological examination shows hyperplasia of the splenic elements such as occurs in ordinary hypertrophic conditions. Nucleated corpuscles showing active karyokinesis may be quite abundant.

The liver is often enlarged, though in some of the cases the size has been found to be normal. It is usually about the normal consistence and color, and the surface of section is smooth. Luzet calls particular attention to the occurrence of cells containing a finely granular protoplasm and irregular, often partly divided nuclei with distinct granulation, or disintegrated nuclei presenting themselves as granular portions scattered within the cell. These cells he looks upon as elements connected with the formation of red corpuscles. The liver cells themselves present no abnormalities.

The lymphatic glands are frequently enlarged, though according to Luzet this enlargement is never conspicuous. It never presents itself in the form of lymphomata such as occur in leukæmia or Hodgkin's disease.

The bone marrow may be diffusely reddened and soft, but extended observations upon this point are wanting.

The *blood* presents striking features. The red corpuscles are invariably reduced, and the oligocythæmia is usually quite marked. In one of v. Jaksch's cases the number was 820,000 per cubic millimetre, and the majority of the cases present figures below 3,000,000. The character of the red corpuscles is altered in correspondence with the degree of anæmia. Von Jaksch called attention to certain forms of protoplasmic degeneration, causing granular or globular formations within the red blood corpuscles, and corresponding to the degeneration of Maragliano, while Alt and Weiss observed distinct poly-

chromatophilia. Poikilocytosis is frequently seen in the severer forms and irregularity in the size of the corpuscles is very marked. The occurrence of nucleated erythrocytes is quite constant, and according to some observers, characteristic. Among others Hayem, Luzet, Alt and Weiss, Hock and Schlesinger have found them very frequently and in large numbers, and have looked upon their abundance as of great diagnostic significance. The small normoblasts are most frequent, but larger forms and even megaloblasts are not unusual. Karyokinetic figures have been repeatedly observed.

The leucocytes are always increased in number and the degree of leucocytosis may be very great. Among the cases collected by Monti and Berggrün five showed from 40,000 to 50,000 leucocytes, three from 50,000 to 65,000, and in one there were 114,150. Regarding the character of the leucocytes, there may be no striking alteration from the normal, though v. Jaksch asserted that polynuclear elements are particularly increased. In four cases studied by Monti and Berggrün there was, on the contrary, a notable predominance of mononuclear forms. The number of eosinophile corpuscles varies greatly, and while v. Jaksch and others state that they are reduced in number, others have found them notably increased (Zappert). The number of leucocytes is liable to considerable fluctuation from time to time.

Nature of the Disease.

It is quite evident from a study of the pathological features, the etiology, and the character of the blood that the anæmia infantum pseudoleukæmica of v. Jaksch, is not an independent disease. It would seem to be, on the contrary, a type of secondary anæmia which may occur in consequence of a variety of affections, and which owes its peculiar characters, and in particular the marked leucocytosis and the number of nucleated red corpuscles, to the age of the patients rather than to an underlying disease.

Symptoms.

The disease is usually gradual in onset, manifesting itself with increasing pallor and weakness. The skin and mucous membranes become pale, and clinical manifestations of anæmia are noted. The child is usually emaciated and in most instances presents evidence of rickets or of congenital syphilis.

The spleen is enlarged and may be distinctly felt projecting beneath the ribs, or sometimes filling the left side of the abdomen. The organ is extremely hard. With improvement in the general

condition and in the state of the blood, the size of the organ gradually or rapidly decreases. Enlargement of the liver may be determined at the same time, though it is frequently absent. When present, however, the enlargement does not correspond to the increased size of the spleen as is the case in leukæmia, and the lower border is sharp rather than rounded. Slight enlargement of the lymphatic glands may be detected, but distinctly projecting tumors are never observed.

Inflammatory complications of various kinds are prone to occur,

Fig. 43.—Anæmia Infantum Pseudoleukæmica (Children's Hospital, Philadelphia).

and death may result from peritonitis, pneumonia, or severe bronchitis.

Diagnosis.

The diagnosis of this condition is usually determined with ease, though its resemblance to leukæmia has frequently led to errors. The points upon which v. Jaksch laid particular stress were the decided reduction in the number of erythrocytes, the marked leucocytosis with increased number of polymorphous leucocytes, and the fact that the liver is not enlarged in proportion with the enlargement of the spleen, while its lower edge is sharp rather than rounded, as is the case in leukæmia. In addition to these facts, the absence of involvement of the lymphatic glands and the unusual abundance of nucleated red corpuscles showing karyokinesis may be of some value, though the latter point requires further confirmation. Hemorrhagic manifestations, such as epistaxis, retinal hemorrhages, and purpura do not occur as in leukæmia. Marked evidences of rickets should always lead to the suspicion that the affection is non-leukæmic. Finally, the course of the disease is more benign, a majority of the cases recovering.

Course and Prognosis.

The course of the disease is more or less progressive, beginning gradually and increasing in severity. Under treatment it tends to a favorable outcome. Among the twenty cases tabulated by Monti and Berggrün death occurred in but four.

Under treatment the leucocytosis subsides, the anæmia gradually improves, and the spleen may decrease until it practically resumes its natural size.

Treatment.

General hygienic measures are of prime importance. The diet must be strictly regulated so as to be nutritious and properly suited to the digestive conditions. In children above the age of one or one and a half years eggs and meat may prove advantageous. In younger children the milk should be properly prepared, and in nursing infants it may be advisable to substitute proper artificial feeding for the mother's milk. Iron in the form of the iodide is useful, but arsenic is of especial value. The latter remedy may be given in the form of Fowler's solution well diluted, and cautiously increased in amount. Inunctions of cod-liver oil and internal administration of the oil with phosphorus have seemed efficacious in some instances.

HÆMOCYTOLYSIS—HÆMOGLOBINÆMIA.

Under the influence of a number of agencies the hæmoglobin of the blood corpuscles may become disassociated from the corpuscles themselves, leaving the latter decolorized as *shadow corpuscles* or broken into irregular fragments. In this removal of the hæmoglobin there may be no chemical change whatever, but more frequently it is met with as methæmoglobin or as other forms.

The hæmoglobin which has been liberated from the red corpuscles may be utilized in different ways in the organism. Undoubtedly there is constant hæmocytolysis taking place in the body and particularly in the liver, and the hæmoglobin liberated in this manner is partly converted into bilirubin and eliminated with the bile. The remaining portion of the hæmoglobin which contains by far the largest amount of iron remains in the body as a pigment substance (hæmosiderin) which is stored in the liver to a certain extent but for the most part transferred to the spleen, the glands, and the bone marrow, where it is doubtless subsequently employed for the production of red corpuscles. More or less serious results may follow the liber-

ation of large quantities of hæmoglobin by hæmolysis. Frequently the white corpuscles are destroyed at the same time and in consequence of the liberation of compounds contained within these, and to a less extent within the erythrocytes, intravascular coagulation and ferment-intoxication may occur. The liberation in the liver of large quantities of hæmoglobin leads to increased thickness and also increased quantity of the bile, which may occasion obstruction of the biliary capillaries and consequent reabsorption by the lymphatics, causing the form of jaundice often spoken of as hæmatogenous jaundice. The investigations of recent years and particularly those of Naunyn and Stadelmann have shown that this is not the result of deposits of blood pigment directly, but rather of reabsorption of altered hæmoglobin from the liver in consequence of the disturbed functions of the latter organ. Frequently irritation of the kidneys results from the circulation of large quantities of hæmoglobin in the plasma, and thrombosis in the blood-vessels or hæmoglobin infarcts in the tubules may take place. Actual nephritis is not unusual in cases of fatal poisoning by many of the hæmolytic intoxicants.

The excess of hæmoglobin in the blood beyond that which may be disposed of by the liver, spleen, and other organs is excreted with the urine, causing the condition known as hæmoglobinuria or more properly methæmoglobinuria. Excess of xanthin bases in the urine or of uric acid is a reliable indication of leucocytic destruction and generally corresponds quite closely with the degree of hæmolysis.

In addition to these irritative symptoms resulting from the liberation of large quantities of hæmoglobin and other cellular constituents, there are manifestations of a functional character due to the inability of the altered hæmoglobins to carry on the proper functions. Among these are dyspnœa, palpitations, cyanosis, and unconsciousness.

Examination of the blood in cases of hæmoglobinæmia may show more or less profound alterations of the red corpuscles. Their number is frequently reduced far below the normal and the number of "shadow corpuscles," or of erythrocytes having distinctly less coloring matter than normal, may be very striking. Irregular fragmentations may be observed, and Ehrlich and others have called attention to the form of degeneration of the red cells in which there is apparently separation of hæmoglobin from the stroma with the production of more or less rounded granules or droplets within the corpuscle. The amount of hæmoglobin in the blood rapidly decreases in correspondence with the amount deposited in the organs or removed from the body. Reduction in the number of leucocytes may take place or there may, on the other hand, be leucocytosis. The alkalinity of the

blood is decreased in consequence of the liberation of phosphoric acid and glycerin-phosphoric acid (Kobert).

Blood Poisons.—A great variety of influences may lead to destruction of the blood corpuscles. These may be classified as those which simply destroy the red corpuscles and liberate the hæmoglobin, those which cause chemical alterations, and those in which there is simultaneously destruction of the corpuscles and alterations of the coloring matter.

Among the causes which liberate hæmoglobin from the corpuscles are the poisons of certain venomous snakes, scorpions, mushroom poisons, arseniated hydrogen, and a variety of vegetables containing poisonous glucosides. Excess of biliary acids in the blood and certain infections, among which malaria and infectious hæmoglobinuria of the newborn are most conspicuous, exercise a similar action. Hæmoglobin is liberated after extensive burns and in cases in which the blood of one animal is introduced by transfusion in the circulation of another of different species. In the latter case the foreign corpuscles are soon destroyed and removed.

Among the poisons which cause an alteration of the hæmoglobin, notably to methæmoglobin, are the chlorates, particularly chlorate of potassium, pyrogallic acid, nitrobenzol, and anilin, as also a number of compounds such as antipyrin and acetanilid. These poisons lead to a dark discoloration of the blood, to disturbances of respiration and cyanosis, and on examination of the blood the spectroscopic peculiarities of methæmoglobin are discovered. Elimination of the hæmoglobin by the urine (methæmoglobinuria) is commonly observed. The symptoms result from the inability of the methæmoglobin to carry on the normal functions.

The poisons of the third group form definite compounds with the hæmoglobin, the oxygen of the oxyhæmoglobin being displaced. Among the more important of these are the combinations of CO and NO with the hæmoglobin, occurring in cases of poisoning by carbonic oxide or nitrous oxide. As in the case of methæmoglobin, the compounds formed are not in themselves toxic, but the effects are due to the inability of the hæmoglobin to perform its normal functions. The results are therefore the same as those of asphyxia. The blood in CO-hæmoglobinæmia is bright red in color, and the spectroscopic features are more or less distinctive, though they resemble closely those of oxyhæmoglobin. The failure of reducing agents to produce reduced hæmoglobin is in itself a distinguishing feature of the condition; but further evidence is furnished by the addition to the blood of ten-per-cent. solution of caustic soda, which causes a cinnabar-red color, while oxyhæmoglobin under the same circumstances becomes

brownish-green. The combinations of H_2S or CN with hæmoglobin occur in poisoning by sulphuretted hydrogen and cyanogen.

Paroxysmal Hæmoglobinuria.

Definition.—This affection is characterized by the discharge of urine containing hæmoglobin or methæmoglobin in paroxysms of variable duration and occurring after more or less well-marked exciting causes. The nature of the disease, however, remains entirely obscure.

History.

The disease was described by Stewart in 1794. Subsequently Dressler in Germany spoke of it under the title of *intermittent albuminuria* and *chromaturia*, and Harley in 1865 described it as *intermittent hæmaturia*. The term *paroxysmal hæmatinuria* was applied by Pavy.

Etiology.

It occurs at all ages, though it is rather more frequently met with in adults. The male sex seems less strongly predisposed than the female sex, although the former is more commonly exposed to the exciting causes. Acquired or congenital syphilis seems to play an important part in the predisposition, and the disease has been noted quite frequently in persons who had suffered severely with malaria or were much reduced by long-standing diseases of various kinds. The most important of the exciting causes is exposure to cold. It has long been recognized that the application of excessive cold, such as freezing mixtures, to even limited parts of the surface of the body may produce hæmoglobinuria in otherwise healthy persons. It would seem that individuals suffering with this disease are much more susceptible and that exposures which ordinarily would occasion little disturbance are capable of bringing on attacks. In some individuals exposure plays a much less prominent rôle, while over-exercise and particularly severe strains lasting for a short time invariably excite a paroxysm. This has been frequently observed in soldiers. The combination of overwork and exposure and particularly exposure to cold water is especially potent. Sometimes none of these influences, however, seems operative, and the attacks are determined only by emotional disturbances, such as anger or fright, or by excessive mental or emotional strains.

Pathogenesis.

Practically nothing is known regarding the nature of this disease. The supposition has been entertained, and is one which naturally suggests itself, that paroxysmal hæmoglobinuria is akin to the toxic and infectious hæmoglobinurias referred to in the chapter devoted to hæmolytic poisons. There has, however, been no proof of this view, and the apparent frequency of the disease in malarious countries is probably largely due to errors in diagnosis, malarial black-water-fever having been mistaken for the disease under consideration. A diminished resistance and a liability, therefore, to destruction of the red corpuscles were assumed by Ehrlich and others in view of the fact that the application of cold to a finger congested by a bandage caused local hæmolysis. It may be urged, however, against this view that certain individuals present the disease in whom exposure to cold has never played a part, and Ehrlich himself has subsequently abandoned his view regarding the diminished resistance of the corpuscles. Chvostek found that the isotonic strength of the red corpuscles is entirely normal, and that the mere influence of cold was of no consequence. In a case under my own observation the isotonicity varied from 0.46 to 0.48, and was therefore normal.

Latterly the opinion has gained ground that paroxysmal hæmoglobinuria is dependent upon nervous influences acting upon the vasomotor system. This view was originally put forward by Mackenzie and has latterly been defended by Murri and others. Chvostek has held that there is a diminished resistance of the corpuscles not to cold but to mechanical influences, and he believes the disease to be the consequence of circulatory disturbances, and particularly contraction of the peripheral vessels with stagnation of the blood in the internal organs following disturbances of innervation. His experimental investigations would seem to give considerable support to this view. The occurrence of paroxysmal hæmoglobinuria in persons subject to attacks of Raynaud's disease is a further point in favor of the view that neurotic disturbances of the circulation are important.

Symptoms.

The onset of the attack may be entirely without premonition. In many cases, however, the patient experiences unusual sensations of fatigue, languor, or the like, and the attack itself is ushered in with rigors or chills and with elevation of the temperature. Frequently the temperature remains normal throughout. Headaches, loss of

appetite, vomiting, and sometimes diarrhœa may be met with, and the characteristic symptom, the passage of port-wine colored urine, soon manifests itself. The quantity of the urine may be normal or decreased; sometimes it is greatly increased in amount. Examination shows the presence of a coagulable albuminous body and spectroscopic examination reveals the absorption bands of methæmoglobin. In seven cases studied by Haliburton this was the only pigment discovered in three, while in the four remaining cases oxyhæmoglobinuria appeared in the latter hours of the attacks. Serum-albumin may occur in greater or less abundance in association with the hæmoglobin. Microscopical examination of the urine discovers few or no corpuscles, but not rarely small masses or concretions of granular blood pigment are discovered, and the cellular elements of the urine may show considerable pigmentation.

The liver and the spleen are frequently enlarged, and the patient may complain of pain in the loins and back.

The duration of the attacks is very variable; sometimes they last but a few hours, in other cases several days. The intervals between the attacks may be considerable in duration—months or even years. In other cases there may be several in a single day.

Alterations of the Blood.—The mass of the blood would seem to be increased during the paroxysms, especially during the rigor at the onset (Grawitz). The plasma is light red in color, showing the presence of dissolved hæmoglobin. Occasionally marked alterations of the red corpuscles may be met with. Among these the shadow corpuscles of Ponfick are particularly interesting and significant; fragmented red corpuscles are much less frequently observed. The hæmoglobin is rapidly reduced in amount during the attack. The leucocytes are little altered. Hayem, Salle, and others have found increased coagulability.

Diagnosis.

The recognition of this disease is usually attended with little difficulty. It is easily distinguished from hæmaturia by the absence of blood corpuscles on microscopical examination. In tropical countries severe hæmoglobinuria due to malarial infection is to be distinguished by the examination of the blood, by the effect of treatment, and by the history of the case.

Other forms of infection and toxic hæmoglobinuria are usually attended by much more violent general manifestations, and the clinical history readily establishes the diagnosis.

Prognosis.

The prognosis of the disease as far as life is concerned is always good, some cases persisting for many years without apparent influence upon the general health. In a recent case under my own observation the patient had been subject to the paroxysms for eight or ten years, and suffered only with the inconvenience of temporary attacks.

Treatment.

The treatment of this condition is most unsatisfactory. A careful study of the case may reveal the causes which are most likely to provoke attacks and the removal of these causes may lead to the cessation of the disease. In particular exposure to cold should always be avoided, woollen clothing should be worn next to the skin at all seasons of the year, and overexercise or nervous disturbances must be controlled as far as possible. During the attacks the patient should be put to bed and should be induced to drink rather large quantities of water or hot drinks. In cases in which a syphilitic history is obtained antisyphilitic treatment is advisable, while in malarial climates quinine in moderate doses may be advisable. It is doubtful, however, whether the latter remedy exercises any influence upon true paroxysmal hæmoglobinuria. After the attacks the administration of tonics and particularly of arsenic is advisable.

PURPURA.

Synonym.—Morbus hæmorrhagicus.

Definition.

The term purpura, derived from *purpureus*, purple, is used to designate a group of conditions marked by hemorrhages of greater or less extent in the skin and unaccompanied by definite disturbances of the general health. Purpuric eruptions occur in the skin in various general diseases, but these are usually referred to as secondary purpuric manifestations or as secondary or symptomatic purpura, to distinguish them from the instances in which the dominating condition in the clinical picture is the purpuric state.

Etiology and Nature.

Hemorrhages in the skin and spontaneous bleeding from the mucous surfaces may occur under a great variety of conditions which

it is necessary to consider somewhat at length that a more exact understanding of the limitations of the term *purpura* may be obtained. A number of writers (Du Castel, Mackenzie, Mathieu, Legg, and Kraus) have classified the purpuric diseases in a more or less similar manner, attempting to find some scheme which would conform with the known pathological data. Following this idea we may distinguish purpuric hemorrhages due to mechanical, toxic, nervous, or infectious influences.

Mechanical Purpuric Conditions.—Not rarely in the course of diseases marked by great cardiac weakness and in conditions in which local obstructions of the circulation have occurred, extravasations take place in the skin of the extremities or in other parts. In such instances the nature of the purpuric manifestations is easily comprehended. An instance of this kind will suffice. A man of forty-five years recently came under my observation with evidences of extreme cardiac asystole, with marked orthopnœa, cyanosis of the lips, and cold extremities. Soon after his admission to the hospital hemorrhagic extravasations made their appearance on the legs, and increased in number and extent until the legs and thighs presented the appearance of universal livid mottling. The spots were purple in color and did not disappear on pressure. At first the ecchymoses were petechial, but later they assumed a somewhat arborescent form, seemingly surrounding the branches of superficial veins. The examination of the heart revealed evidences of mitral stenosis and regurgitation. At first it was thought that the hemorrhages might be embolic and due to malignant endocarditis; but the subsequent changes in the extravasations and the autopsy showed that they were entirely mechanical, though perhaps some previous toxic alterations of the vessel walls might have occurred and rendered the rupture of the vessels easy.

Mechanical purpura of still more undoubted character is sometimes seen to result from massage in persons having a thin skin and rather hairy surface, or in cases in which ecchymoses appear upon the limbs in consequence of the obstruction of circulation resulting from varicose veins.

In the same group may be placed the purpura of the aged or *purpura senilis*. In these cases hemorrhages occur in the skin of the legs and arms or elsewhere, without the least disturbance of the health before, during, or after the attack. Doubtless the changes of involution in the vessels (senile atrophy) or atheroma together with retarded circulation play an important part in such cases. In a measure such cases are toxic, as doubtless the vascular changes are frequently the result of slowly developed toxic disturbances, but at

the time of the hemorrhage the manifestations are mechanical in character.

Toxic Purpuric Conditions.—The simplest and best known cases of this group are those in which purpuric hemorrhages follow immediately upon some form of drug intoxication (*purpura medicamentosa*). Among the substances capable of causing these results are phosphorus, iodine, iodide of potassium, the salts of mercury, nitrate of silver, chloral, chloroform, kairin, antipyrin, and many other medicinal agents. An instance of this kind having striking features came under my observation a few years since. A woman suffering with uræmia presented a marked purpuric eruption and bled profusely from the gums and other mucous surfaces of the mouth, some time after the uræmic manifestations had subsided and quite soon after she had received large doses of calomel (gr. xv.) as a diuretic. The case was not clearly one of toxic (medicinal) purpura, but it was highly suggestive. The local or distant purpuric hemorrhages which occur after poisoning with the venom of serpents, scorpions, or other animals need only be alluded to.

Another group of cases is of much greater clinical and pathological interest—that in which the hemorrhages are among the effects of intoxication with poisons generated by the activity of microorganisms or by other processes within the human body itself. It is difficult to estimate the extent to which the toxins are active in the hemorrhages which occur in various infections diseases, but certainly it is the chemical poisons and not the bacteria themselves, in at least some of the cases. Experimentally it has been proved repeatedly and for various forms of bacterial products that they are capable of producing hemorrhages. In these cases acute degenerative lesions of the blood-vessels or of the tissues immediately adjacent to the vessel walls are the first effect of the intoxication, the hemorrhages being a secondary result. Doubtless in some instances alterations in the blood itself are first occasioned and this may be an important contributing cause of the hemorrhages, but the tendency of the present time is rather towards the view that vascular and tissue changes are more important than alterations in the blood. Tissue destruction and perhaps also blood destruction under the influence of bacterial poisons may, however, lead to thrombosis in the smaller vessels (white thrombi, hyaline thrombi) and thus to secondary mechanical hemorrhages.

A third group of toxic purpura is that which occurs in various chronic or cachectic diseases (*purpura cachectica*). Instances of this character are seen in cases of carcinoma, chronic nephritis, syphilis,

amyloid disease, and hepatic affections attended with biliary poisoning; and perhaps it is proper to include the hemorrhages of pernicious anæmia, Hodgkin's disease, and leukæmia. In all of these diseases apparently spontaneous hemorrhages may occur in the skin or elsewhere, and in the analysis of the probable causes it would appear most likely that toxic agents acting first upon the blood-vessels are the important etiological factors. In some of the conditions named (nephritis, syphilis, amyloid disease) changes in the blood-vessels are well known and the cause is quite generally recognized to be poisons generated in the course of the disease; in the other forms of marantic or cachectic purpura a similar pathogenesis may be assumed in many instances. It is not unlikely, however, that obstruction of the vessels by thrombi or by cellular masses (leukæmia) may contribute to the occurrence of the hemorrhages in certain instances.

Infectious Purpuric Conditions.—That many instances of purpura (using this term in its broadest descriptive sense) are infectious has long been recognized. Allusion need only be made to the hemorrhagic manifestations occurring in some cases of scarlatina, measles, small-pox, typhoid fever, anthrax, and other infectious fevers. To these cases the distinguishing terms, *purpura scarlatinosa, morbilosa, variolosa, etc.*, have been applied, and the cause of the hemorrhage is recognized to be the infectious agent in the several diseases or the chemical products of these. The modern teaching of bacteriology leads to a ready acceptance of hemorrhages, of greater or less extent, as lesions common and quite significant in nearly all forms of infection. Experimental proof of this fact was furnished as early as 1822 by Gaspard, who showed that purpuric manifestations could be caused by injections of putrid matter. In recent years observations of this nature have been repeated in every laboratory, not only with putrid materials but also with pure cultures of various bacteria. In addition to these facts and approaching more closely to the present subject, experimental evidence has not been wanting that purpuric manifestations may be caused in animals by direct inoculation with blood from affected persons. Thus Ceci among others injected the blood of a woman presenting indefinite symptoms, together with purpuric manifestations, into animals, and was thus able to reproduce the hemorrhagic phenomena.

Finally, direct bacteriological examinations have shown the presence of various forms of micro-organisms in cases presenting the clinical features of purpura hæmorrhagica, either with or without antecedent local diseases. Among the instances in which the purpura has associated itself with other diseases may be noted cases of

malignant endocarditis, pseudomembranous or suppurative forms of pharyngitis and tonsillitis, various forms of local suppurations, as abscess, cellulitis, suppurative osteomyelitis, phthisis with cavities, suppurations of the umbilicus in the newborn, and the like. Among the organisms detected in such cases the most frequent have been streptococci, staphylococci, pneumococci, and the bacillus pyocyaneus. Instances of this kind are generally classed as cases of *secondary, symptomatic, or infectious purpura,* in contradistinction from the forms in which no antecedent disease is recognized and in which the term *primary or idiopathic purpura* is used. The latter, however, are undoubtedly in most if not all cases infectious in nature, as may be determined from the nature of the lesions observed, the evident widespread character of the systemic affection, the clinical course of the disease, and the direct evidence of bacteriology. Of the lesions the hemorrhages are most significant, as in experimental forms of infection, and the distribution of the disease evidently follows the vascular system in all parts of the body. The onset of the disease after prodromal symptoms of variable duration and the clinical manifestations are further evidences of the nature of the condition, while in some instances local epidemics and even probable contagiousness have been observed. An interesting instance favoring the last point was reported by Lingen. A pig was taken ill with "Irish purpuric disease," exhibiting purpuric spots on its belly, face, and nose before its death. A servant girl who attended to the pig was attacked with febrile symptoms and was ill several weeks, while the owner of the pig had suffered, presenting large purpuric spots on the loins and thighs, and smaller ones elsewhere. The cowman died in three days of a similar attack. Instances of this character might be multiplied; but sufficient is known regarding these conditions to lead to the firm conviction that purpura is an infectious disease or group of diseases, the source of infection being obscure; that, in other words, it represents a form of cryptogenetic sepsis. Further investigations may clear up the question of the original source, but hitherto bacteriological studies have been successful only in discovering micro-organisms in the blood and in the tissues. In several cases studied by Kolb short thick bacilli, pathogenic for mice, were discovered in the blood and tissues, and somewhat similar organisms were found by Tizzoni and Giovanni, Victor Babes and others. Letzerich described bacilli resembling the anthrax bacillus in appearance. Klebs, who was one of the first to develop the idea of infection, found a round body which he termed "Monas hæmorrhagicum," in cases of "hæmophilia of the newborn." More recently micrococci, especially streptococci, have been found by a number of

investigators, including Ceci, de Grimard, Guarnieri, Cheyne, Rohrer and Hlava, Vassale, and others.

It must be admitted then that micro-organisms play the most prominent rôle in the development of purpuric conditions of various kinds. In some instances there are definite antecedent conditions to which the infection may be traced, and the term secondary purpura may be applied to such. In other cases the sepsis is cryptogenetic, and for the present we must be content to accept the clinical classification of primary infectious purpura.

The manner of action of the bacteria in question remains in doubt, though in some cases definite lesions have been determined in the blood-vessels. Among these changes Babes has found hyaline degeneration of the walls of the vessels; Wilson and Grainger Stewart amyloid degeneration; Hayem and others proliferative or desquamative endarteritis or similar processes in the capillaries, leading to local weakening or to obstruction with consequent overdistention and rupture on the proximal side. Accumulation of leucocytes or hyaline thrombosis has been observed by Hayem, Ollivier, and Ranvier, and bacterial embolism is doubtless very frequently the immediate cause of hemorrhage. It was demonstrated by Cheyne, Baumgarten, and others, and is commonly observed in experimental investigations. The local weakening of the vessel walls or the distention on the proximal side of the obstruction may be the immediate cause of hemorrhage in these cases. The tendency at the present time, however, is to ascribe important functions to the chemical products of bacterial growth, and without doubt degenerative weakness of the blood-vessels is often produced by the toxins.

Nervous Purpuric Conditions.—The influence of the nervous system in the production of hemorrhage has long been recognized by clinicians. In this connection the interesting condition known as stigmatization is important. A number of celebrated instances of this have been reported and carefully studied, while innumerable instances of less striking character have been observed. It occurs in neurotic and mostly ecstatic persons and is marked by the occurrence of hemorrhage from the unbroken skin in the situations corresponding to those of the wounds at the crucifixion. During the periods when the manifestations present themselves the patients are usually in a state of great excitation or ecstasy, and the occurrence of the attacks bears a close relation to the neurotic state of the individual. According to Garres the first instance of this kind was that of St. Francis of Assisium, who was born in 1186 and died in 1236. In 1224 the most notable attack occurred, and in celebration of this occurrence Pope Benedict XI. made the 17th of September the Feast of the Holy

Stigmata. Another case occurred in 1242 near Cologne, that of Christine de Stumbele. The most celebrated cases, however, are those of Palma d'Oria (born in 1805) and Louise Lateau (born in 1850). Palma d'Oria had seen the latter in one of her attacks, which began in 1868, and became affected herself in 1871. The frequency of the condition is evidenced by the fact that Imbert-Gourbeyre collected one hundred and fifty-three instances; and in the literature of the last ten years I have noted a number of distinct cases.

Aside from these remarkable cases neurologists have frequently called attention to the hemorrhages occurring in areas in which neuralgic pains have existed, and to the occurrence of hemorrhages in the painful crises of various nervous diseases. Further, it is not infrequent to find large or small hemorrhages in the stomach or lungs in cases of cerebral hemorrhage, epileptiform convulsions, and other nervous affections involving the brain. These conditions have been particularly studied by Jahn, Charcot, Schiff, and Ebstein, and Schiff in particular showed that hemorrhages in the stomach could be induced by injury of certain parts of the brain. It is undoubtedly true that nervous influences may determine hemorrhages in the skin or elsewhere, but it is scarcely probable that such influences are of importance in cases of purpura.

Having considered the various etiological factors that may have influence in the occurrence of spontaneous hemorrhages, it remains to classify somewhat more systematically the hemorrhagic diseases as they present themselves to the clinician. At the present time it is possible to establish only partly satisfactory groups. All of the cases may be divided into secondary and primary forms. Among the first are infectious, mechanical, and toxic cases, including in the first subdivision the purpuric forms of scarlet fever, small-pox, etc.; in the second the purpuric conditions of cardiac disease, atheroma, and the like; and in the third the form occurring in jaundice, cachexias, etc. A neurotic form might be included, but in cases of nervous disturbances the hemorrhages are rarely of distinctly purpuric type. Of the primary forms of purpura there are the purely toxic or medicinal purpuras in which the poisons are introduced from without the body; and second, forms due to septic infection and intoxication and in which mechanical or nervous influences may aid in determining the seat and extent of the manifestations. A third form (hæmophilia) is probably due to congenital disease of the vessels or blood, and its manifestations are therefore of a mechanical nature.

To classify these forms in tabular manner we may construct the following scheme:

A. Secondary Purpuric Conditions.
   1. Infectious: Scarlatina, variola, typhoid, etc.; infectious hæmophilia of the newborn; septic purpura in pseudomembranous pharyngitis, cellulitis, osteomyelitis, etc.
   2. Mechanical: Cardiac, atheromatous, purpuric ecchymoses in phlebectasia, mechanical embolism, etc.
   3. Toxic: Autointoxications; jaundice, pernicious anæmia, cachexia.
   4. Nervous: Hysteria, lesions of the brain, etc.

B. Primary Purpuric Conditions.
   1. Septic infection and intoxication: Cryptogenetic infection; purpura, scurvy.
   2. Toxic (purpura toxica et medicamentosa): Snake-venom, iodine, mercury, etc.
   3. Mechanical: Hæmophilia.

Finally, it remains to consider the clinical classification of the form of primary purpura which we assume to be of the nature of cryptogenetic sepsis. This term or subdivision includes the conditions ordinarily termed purpura; and doubtless it may be asserted that a number of distinct forms of disease are included or that, in other words, purpura is a term (even in the restricted application here given to it) designating symptom groups rather than definite diseases. Willan included four groups: Purpura simplex, purpura hæmorrhagica, purpura urticans, and purpura senilis. This classification, however, is inapplicable at the present time. The distinguishing feature of purpura urticans is too slight to warrant the use of this term to designate a special group; while senile purpura is either a secondary purpuric condition traceable to distinct antecedent conditions (atheroma, cachexia, etc.), or it may be included with purpura simplex. For practical purposes we may consider three forms: one in which the purpuric eruption is the dominating symptom, a second in which joint manifestations are conspicuous, and a third characterized by free hemorrhages. To these the terms purpura simplex, purpura rheumatica, and purpura hæmorrhagica may be applied; but attention is once more called to the fact that no sharp dividing line can be drawn, and that in all likelihood each group may contain different forms of infection, some of which resemble those of another group, though differing from those of its own clinical subdivision.

The attempt has been made to include scurvy and hæmophilia

with purpura. The former of these conditions is undoubtedly closely allied to some of the cases of primary purpura, but its manifestations are sufficiently marked to warrant its retention as a distinct clinical entity. In hæmophilia evidence is wanting to show that it bears close relations with either scurvy or primary purpura, and for the present we must look upon it as a disease dependent upon some congenital deficiency of the vascular mechanism or of the blood. It will now be necessary to consider the individual forms of purpura separately.

Purpura Simplex.

Etiology.

The special etiology of this form of purpura is obscure. It occurs quite commonly in anæmic and ill-developed individuals and sometimes makes its appearance during convalescence from diseases which have depressed the vitality greatly. Graves pointed out the association with diarrhœa, and in some instances evidences of the rheumatic diathesis are obtained. Purpuric eruptions occur in the aged and among the insane with considerable frequency and may be classed as purpura simplex rather than with other forms, though the special term, *purpura senilis*, has been applied to the form occurring in the aged. In these instances small purpuric spots appear upon the extremities or upon the body from time to time, and are unaccompanied by other manifestations. It is quite likely that the etiology in such instances is very different from that of the purpura occurring in younger individuals and in those apparently in good health.

Symptoms.

Purpura simplex is characterized by the development of small petechiæ occurring upon the legs or other parts of the body. These are usually very small in size and discrete, though occasionally they become confluent and cover considerable areas of the skin. The surface is as a rule entirely smooth, no elevation of the skin at all appearing at the seat of the lesion (*purpura maculosa*). Sometimes the infiltration of blood is more considerable and elevation of the surface takes place, small papules being thus formed (*purpura papulosa*). Occasionally urticarial wheals are also seen, but these are more frequent in the form of purpura next to be described.

The eruption of purpura simplex generally begins upon the extensor surfaces of the legs near the ankles, but in severe cases spreads to the thighs, to the trunk, and to the arms. The face is

rarely involved. The spots are at first bright red in color and do not disappear on pressure. Subsequently they change to a dark-brownish color, then to a green, and finally to a yellow, the alterations in color resembling those seen in the "black-and-blue" marks of bruises. In rare instances small vesicles may form and may contain either a clear serous or a sanguinolent fluid.

In many cases the patient presents no other symptom and, excepting the appearance of the eruption, no suspicion of illness would be entertained. In other cases there is a mild febrile movement together with some disturbance of digestion and general weakness. The appetite is poor, the patient is easily fatigued, and increasing pallor may be noted. Slight swelling of the joints is sometimes observed, but this is more characteristic of the next form to be described, purpura rheumatica. The examination of the blood shows no characteristic features, and this fluid may appear to be entirely normal to the ordinary clinical examination.

Course and Prognosis.

The eruption may occur in a single crop and the disease may terminate without further manifestations. More commonly repeated crops of eruption are observed and the duration is thus protracted. As a rule a single attack occupies only a few days or a week or two at most, but relapses are not infrequent and the patients may suffer repeated attacks, lasting for months or even years. As a rule the prognosis is entirely favorable. Cases, however, have been observed in which the disease has occurred abruptly, has run a rapid course and terminated fatally in from one to four days. Such cases, however, are more commonly of the type of purpura hæmorrhagica under which title they will be more fully described.

Purpura Rheumatica.

Synonym.—Peliosis rheumatica (Schönlein).

Definition.

This condition is characterized by a purpuric eruption upon the skin, by moderate fever and painful swellings of the joints, and sometimes by sore throat or abdominal colic.

Etiology.

The disease is especially frequent in the male sex and as a rule affects individuals between the ages of fifteen and thirty-five years. Delicate individuals and those whose vitality has been lowered by

previous diseases, such as a malaria, tuberculosis, and other chronic affections, seem particularly predisposed, though it may make its appearance in persons apparently healthy. It is more frequent in the winter months and seems to be more common in cold climates than in warmer regions.

The names applied to the disease indicate its supposed relationship with rheumatism. In some instances a distinct rheumatic history is obtained and patients who have suffered with attacks of rheumatism may subsequently present purpura rheumatica. This, however, is by no means invariably the case. In two instances under my own observation there had been no evidence of rheumatism and not even a tendency to tonsillitis. In another case, however, the development of the disease followed immediately upon an attack of tonsillitis. In the same connection it is interesting to note that some authorities have classed cases of malignant endocarditis with purpuric eruption of the skin as instances of purpura rheumatica, but such a view is no longer entertained. It is impossible to determine at the present time whether or not this disease actually bears a direct etiological relationship to rheumatism, since in neither disease specific causes have been discovered. It cannot, therefore, be asserted that they are identical in etiology, though it is likely that both result from allied forms of infection and possibly often from the same infective cause.

Eichhorst refers to a case of purpura rheumatica in association with gonorrhœa, and Litten has recently called attention to the same condition. Such cases must be looked upon as instances of symptomatic infectious purpura. In women the disease sometimes makes its appearance just before the menses.

Pathological Anatomy.

The lesions met with in purpura rheumatica are of indefinite character. Hemorrhages are found beneath the skin and occasionally the internal organs may show punctate extravasations. The joints contain clear synovial liquid, while the synovial membranes themselves are congested or infiltrated with extravasated blood. Small hemorrhages have been found in the muscles, but larger extravasations of blood are not observed.

Symptoms.

The onset is usually gradual. A prodromal period of several days to several weeks generally precedes the more acute symptoms of the disease. The patient becomes weak and depressed, suffers with a mild febrile movement, and complains of loss of appetite. Occasion-

ally, as in the case already noted, the disease begins with the ordinary manifestations of sore throat. The actual onset of the disease itself is marked by stiffness and pain in the muscles and by pain in the joints. The ankle and the knee joint are usually first affected and these alone may be involved. The affected parts become swollen and often are reddened and hot, the appearance of the joints being that seen in the milder forms of acute articular rheumatism. The swelling and other manifestations about the joint usually remain localized throughout the attack, and when other joints are affected those first involved are uninfluenced by the secondary extensions.

Coincidently with the affection of the joints or sometimes after the latter, a purpuric eruption appears upon the skin, this being more common upon the extensor surface of the legs, as in the case of purpura simplex. In the cases under my own observation the eruption has been most abundant in the vicinity of the affected joints, but it may extend to a considerable part of the entire surface of the body. The lesions are usually small, petechial in character, and do not, as a rule, show any tendency to become confluent. Occasionally, however, confluence is observed, and large patches the size of a dollar or even as large as the palm of the hand may develop. Not rarely the skin between the purpuric spots is elevated and œdematous, forming urticarial wheals, this association of urticaria and purpura having received the name of *purpura urticans*. In other cases nodular infiltrations indistinguishable from *erythema nodosum* may be observed, or the lesions of *erythema exudativum* may be combined with the petechial eruption. Vesicles may form upon the surface, especially in cases in which the petechiæ are confluent and blebs of considerable size filled with clear or with bloody liquid may be thus occasioned (*pemphigoid purpura*).

Œdema of the feet and ankles is frequently seen and sometimes reaches a considerable degree. In other cases œdematous swelling is observed about the face or in the loose cellular tissues of other parts. The term *febrile purpuric œdema* has been applied to cases in which considerable œdema, especially about the face, has been associated with the febrile form of purpura.

The general condition of the patient is usually one of depression. The appetite is poor and anæmia is developed with considerable rapidity. The temperature usually ranges from 99° to 103°, but is irregular in type and may disappear before the other symptoms of the disease have subsided. Gastrointestinal disturbances may make their appearance, though they are usually mild, except in the form of purpura in children, presently to be described; the urine is frequently albuminous, but actual nephritis is uncommon.

Complications.

Cardiac lesions have occasionally been observed as in the case of Musser and Osler, in which endopericarditis was associated and in which the suspicion at first arose that the case was one of ulcerative endocarditis with extensive infarcts in the skin. Inflammatory complications of the other serous membranes are unusual. Hemorrhages upon the mucous surfaces are usually absent, but occasionally ecchymoses have been seen, and Kaposi records an instance in which hemorrhagic extravasations followed by gangrene were seen in the mucous membrane covering the palate. Still more rarely large hemorrhages from the mucous surfaces (such as hæmaturia, epistaxis, and the like) have been recorded. Such cases, however, belong more properly in the group of purpura hæmorrhagica.

Course and Prognosis.

The duration of the disease is extremely variable. Sometimes after a week or two the purpuric manifestations and the swelling of the joints subside, and the patient recovers completely. In other cases a protracted convalescence may be noted, and relapses are prone to occur if the patient leaves his bed too early or engages at once in his usual occupations. Sometimes repeated relapses cause a continuance of the disease for months or years. The prognosis is usually favorable excepting when definite complications have developed.

Diagnosis.

The characteristic symptoms of this form of purpura are the petechial eruptions, the swelling of the joints, the tendency to urticaria, and the fever. In some cases, as in the one already alluded to, it may be difficult to exclude malignant endocarditis. In this affection swelling of the joints with tenderness and purpuric eruptions are not uncommon, but the existence of a distinct cardiac lesion and the secondary development of purpura usually render the diagnosis easy.

The diagnosis from rheumatism is made by the manifest purpuric character of the affection, by the distinct prodromal symptoms, and by the fact that the joint manifestations are usually much less severe and much less prone to pass from joint to joint than is the case in true rheumatism. The extreme sweating of rheumatism is less prone to occur, and cardiac complications are much more unusual.

Henoch's Disease.

Henoch has described a form of purpuric disease which occurs in children more commonly than in adults, and which may with greater propriety be included under the head of purpura rheumatica than with any of the other forms.

It is characterized by marked gastrointestinal symptoms, by slight swelling of the joints, by purpura, and by renal symptoms. The abdominal symptoms are usually extremely severe. Vomiting and diarrhœa are nearly always present, and extreme gastric pains coming on paroxysmally and sometimes with especial severity at night give the disease its most striking characteristics. The purpuric eruption occurs in the form of small petechiæ or as purpura urticans and the ecchymoses as a rule make their appearance in separate crops at intervals of one or more days. The older spots sometimes fade to a yellowish color before the more recent ones have made their appearance. Occasionally the diarrhœa assumes the character of melæna. The abdomen is swollen and becomes extremely tender. The urine is nearly always albuminous and may contain abundant casts and blood. Death may occur after a short time or the disease may be protracted, the patient eventually succumbing to the repeated intestinal attacks or to the nephritis.

Purpura Hæmorrhagica.

Synonym.—Morbus maculosus Werlhofii.

History and Definition.

This disease was described by Werlhof in 1775, though previous observations had been made by Zeller in 1694, and probably by others at still earlier periods. The disease is characterized by spontaneous hemorrhages affecting the skin as in all of the forms of purpura, but in addition the mucous membranes and the internal surfaces are involved, and more or less extensive hemorrhages from the mucous tracts are commonly observed.

Etiology.

It occurs more frequently in women than in men, and as a rule in young persons. It is ordinarily considered to be a very rare disease in the newborn, though hemorrhagic manifestations in children are not unusual. Dreschler observed the disease in a child of five months

and Dohrn is stated to have seen it in a newborn infant. In a child aged four days, under my own observation, extensive hemorrhages occurred in the skin, the mucous membrane, and the internal organs, and the child died of excessive hemorrhages from the stomach and bowels. There were no evidences of septic infection and bacteriological examination of the tissues gave negative results. Such cases may be grouped with the *infectious hæmophilia of the newborn* of Klebs and others, but may with equal or perhaps greater propriety be described as forms of hemorrhagic purpura.

The previous health exercises no definite influence upon the occurrence of purpura hæmorrhagica, though the disease is supposed to occur more frequently in those of delicate constitution or in persons weakened by disease. Like the other hemorrhagic diseases, it appears to be more frequent in northern countries and along the sea coasts, and the attacks are more frequent during the colder parts of the year.

The surroundings of the patient are of considerable importance. Individuals exposed to cold, living in damp houses, subjected to bad diet, and particularly such as are crowded in institutions, like almshouses, prisons, or asylums, suffer in their general vitality in a manner that renders them more liable to the disease than are those whose surroundings are entirely comfortable and sanitary.

Occasionally the disease occurs in the convalescence of infectious disease, such as typhoid fever, scarlet fever, and malaria, and among the diseases supposed to predispose to its occurrence syphilis and tuberculosis may be enumerated.

Various toxic agencies, such as iodide of potassium, preparations of mercury, phosphorus, silver and other mineral poisons, sometimes give rise to manifestations resembling those of idiopathic hemorrhagic purpura.

Infection.—Reference has already been made in the general remarks upon purpura to the likelihood of all of these forms of disease being infectious in nature. This is particularly the case in purpura hemorrhagica, and organisms have been found in the blood and in the tissues by a number of observers. No definite and specific bacterium has, however, been isolated, and it is doubtful whether the infection in all cases is the same.

Pathological Anatomy.

The organic changes in this affection are by no means characteristic. The internal organs are frequently pale when the loss of blood has been considerable enough to produce general anæmia. The most

striking lesions are the small or large petechiæ, or extensive extravasations, the color varying from a bright red to a light brown or yellowish-green. The subcutaneous tissues, the intermuscular septa, and the periosteum of the bones in contradistinction to the conditions found in scurvy are ordinarily free of extravasations, though small punctuate hemorrhages in the muscles are sometimes observed. The mucous membranes are rarely free, and in the mouth there may be more or less extensive infiltrations affecting the gums or other parts of the mucosa. The serous surfaces usually present petechial ecchymoses, but larger effusions or inflammatory changes are quite unusual. The spleen and the lymphatic glands are often enlarged and may contain an excess of blood pigment, the latter being particularly true of the lymph glands in the vicinity of hemorrhagic extravasations.

The blood itself presents no distinctive features. After large hemorrhages there is, of course, a reduction in the number of red blood corpuscles, and this may be of considerable amount. At the same time moderate leucocytosis develops as in other cases of hemorrhage. In two of my cases the relative excess of lymphocytes was quite striking. Ordinarily when the hemorrhages have not been severe, the number of red corpuscles is from 2,500,000 to 4,000,000; after excessive hemorrhages the number may fall as low as 1,000,000 or even less. The hæmoglobin is usually reduced more strikingly than the number of corpuscles, and particularly is this noted during the stage of convalescence since, as in other conditions, the corpuscles regenerate more rapidly than the hæmoglobin (Kahler, Otto).

Symptoms.

The onset of hemorrhagic purpura is often extremely abrupt and violent. In one of my cases in which two distinct outbreaks occurred with an interval of several years intervening, the first symptom was furious epistaxis which exsanguinated the patient and reduced him to the last degree, and was preceded by no manifestation or premonition of any kind.

In many cases, however, prodromal symptoms are present, and, as Letzerich has pointed out, this stage of the disease may be of considerable duration. Among the symptoms noted, weakness and loss of appetite are generally the most frequent. The patient may, however, complain of gastric pain, heaviness after eating, evidences of disturbed digestion, constipation, febrile attacks, or nervous disturbances such as vertigo, ringing in the ears, and the like. The prodromal stage, however, is never marked by pronounced symptoms.

The first distinct evidence of the disease is usually the occurrence of hemorrhages in the skin. These appear on the legs or the ankles, and especially upon the extensor surfaces, and later involve the thighs, the arms, the buttocks, and the trunk. The face is rarely involved. The eruptive process occurs in the form of small petechiæ or of larger ecchymoses. The pressure of the clothing or traumatism may determine more extensive extravasations; and sometimes, either spontaneously or following injury, considerable masses of extravasated blood may collect in and beneath the skin. The entire surface may be covered and the skin may acquire a curious mottled appearance, especially in the later stages when the changes in color characteristic of extravasated blood have made their appearance.

Urticaria, such as occurs in rheumatic purpura, and vesicles or blebs may form upon the surface; sometimes the extravasated blood undergoes suppurative change, and necrosis or gangrene of the skin is occasionally seen.

The mucous membranes are affected with about equal frequency and usually at about the same time as the skin. The commonest and often the first symptom is epistaxis, the loss of blood in this manner sometimes being enormous. The nasal mucous membrane usually presents ecchymotic extravasations even in cases in which actual hemorrhage from the nose has not occurred. The mucous membrane of the mouth is frequently involved and the gums may become violaceous in color and show considerable swelling, but the actual necrosis or ulceration observable in scurvy is rarely, if ever, present in purpura hæmorrhagica. Hæmatemesis and hemorrhages from the bowel are not uncommon, and may be attended by decided gastro-intestinal disturbances. Hæmaturia has been observed and is sometimes the only manifestation of the hemorrhagic tendency, as in the form of renal purpura hæmorrhagica described by Senator.

Hemorrhages upon the serous surfaces and into the serous sacs may occasion marked symptoms. Very frequently the joints become swollen and somewhat painful, the knee-joint and elbow-joint being particularly prone to be affected. Considerable inflammatory change in the joints, however, is rare.

Hemorrhages into the membranes of the brain sometimes occasion violent cerebral symptoms, such as unconsciousness, epileptiform attacks, and localized or widespread palsy.

Extravasations of blood may occur in the conjunctiva, the retina, or the choroid. These may occasion no disturbance of vision even though quite extensive; but, on the other hand, considerable amaurosis is observed in some instances.

The general condition of the patient may be little disturbed.

Sometimes indeed the lack of general symptoms is most remarkable despite the occurrence of severe and protracted hemorrhages. Usually, however, pallor and weakness with increasing anæmia are observed and the patient complains of cardiac palpitations, of dyspnœa, and of a feeling of faintness on slight exertion. Actual syncope is not uncommon and is ascribable to the reduction in the blood mass and the weakened circulation consequent upon the excessive hemorrhages. The temperature may be normal or subnormal throughout the entire attack, but in most instances slight elevations of temperature are observed from time to time, and occasionally the degree of fever is considerable, amounting to 103° or even 105°. Albuminuria is often discovered, but tube casts and other evidences of nephritis are unusual. Physical examination of the heart and of the circulatory system generally reveals some enlargement of the cardiac chambers and functional murmurs may be heard at the base of the heart; while humming murmurs in the veins and visible pulsation of the veins are nearly always observed in instances in which the loss of blood has been considerable.

Purpura Fulminans, Henoch.

A form of purpura hæmorrhagica of violent character, to which allusion has previously been made, is appropriately considered in this place. This form of purpura, as the name indicates, is extremely acute in its onset and rapid in its course. Hemorrhages occur with particular frequency in the skin in the form of ecchymoses which tend to become confluent, and as hard infiltrations. Vesicles and blebs filled with clear serum or hemorrhagic fluid not rarely form upon the surface, and sloughing of the skin may sometimes occur when the disease is of sufficient duration to permit of this change. The internal organs are rarely affected and hemorrhages from the mucous membrane are unusual, probably because the rapidity of the disease gives too little time for the full development of the hemorrhagic manifestations. Fever may be absent, but in most cases it is present and sometimes it reaches unusual degrees. Examination of the urine usually shows the presence of albumin. The cases run a rapid course and prove fatal in from one to four or five days.

In most instances the disease is idiopathic, but occasionally it arises in association with pneumonia, scarlet fever, and other infectious processes.

Course.

The duration of the ordinary form of purpura hæmorrhagica varies greatly. The individual attacks usually occupy from two to

five weeks, but the course of the disease may be much more protracted by the occurrence of relapses, and the entire duration may be one of many months. Frequently the same individual is affected at intervals of several months or years, his condition in the intervening time being apparently entirely normal. The cases of purpura fulminans to which reference has already been made prove fatal in a few hours or days.

Complications and Sequelæ.

Complications upon the part of the internal organs have already been referred to. The most important are those arising from the hemorrhages into serous cavities. Pneumonia and œdema of the lungs may be the immediate cause of death in some instances. Among the sequelæ palsies resulting from the hemorrhages into the membranes of the brain are sometimes observed. Fagge refers to the occurrence of visceral sarcoma following the disease.

Diagnosis.

The recognition of purpura hæmorrhagica is never difficult. It is, however, a matter of considerable difficulty to distinguish certain specific affections in which purpuric manifestations are met with, from simple purpura hæmorrhagica. In recent years a number of instances have been recorded of acute leukæmia and acute pseudoleukæmia in which the onset of the disease was marked by the clinical manifestations of purpura hæmorrhagica, and the cases have been recorded as instances of this disease until the examination of the blood or the development of specific lesions in the lymphatic apparatus have made the differential diagnosis possible. The examination of the blood in these cases usually establishes the diagnosis of leukæmia, though this disease may begin with the stage in which the excess of leucocytes is not observed. Pseudoleukæmia beginning in the form of purpura hæmorrhagica offers greater difficulties, and the diagnosis can only be made by the discovery of distinct enlargements of the glands or of the spleen.

From purpura simplex and purpura rheumatica the diagnosis is made by the fact that the hemorrhages in the disease under consideration are more severe and in particular by the occurrence of large hemorrhages from the mucous membranes. In addition to this the manifest disease of the joints of purpura rheumatica is usually absent in the hemorrhagic form, though some enlargement and tenderness of the joints may be observed. The distinction from scorbutus can be made by the absence of changes in the gums, and by the fact

that deep-seated hemorrhages, especially those in the muscles, in the intermuscular tissues, and in the flexures of the joints are usually absent in purpura hæmorrhagica.

The differential diagnosis between hæmophilia and this disease sometimes offers great difficulty. Particular attention will be called in the discussion of hæmophilia to the form of spontaneous hemorrhage occurring in the newborn, and affecting the gastrointestinal tract, the skin, the umbilicus, and the mucous membrane of the nose as well as other parts, and in which a history of a hemorrhagic diathesis cannot be obtained. Such instances have variously been termed hemorrhagic disease of the newborn, infectious hæmophilia, and the like. In the clinical manifestations they resemble purpura hæmorrhagica and cannot be readily distinguished from this condition. They are distinguished from hæmophilia, however, by absence of the hereditary tendency, and by the fact that hemorrhages from the umbilicus are more frequently met with than in the latter disease and that jaundice is more commonly observed.

Certain of the acute infectious diseases at times make their appearance with violent hemorrhagic manifestations and cannot easily be distinguished from hemorrhagic purpura. Among these small-pox, scarlatina, diphtheria, and typhoid fever may be noted. In one instance of the last-named disease under my own observation death occurred from severe epistaxis and hæmatemesis in the early part of the second week of the disease and before the symptoms had been distinctive. The post-mortem examination alone determined the existence of typhoid fever, the lesions being unmistakable.

Occasionally toxic purpura resembles the idiopathic disease in every particular, as in one case in which the disease developed in a patient suffering with uræmic manifestations after the subsidence of the latter, and apparently in consequence of excessive doses of calomel used for their diuretic action. The history of such cases alone can establish the probable cause of the manifestations.

Prognosis.

The prognosis must always be made with extreme care. It is impossible to determine beforehand in a given case what the progress of the disease will be. The most extensive hemorrhages frequently occur without the slightest warning. In all cases, however, in which severe hemorrhage has begun or in which high fever and profound constitutional depression are present, the prognosis is most unfavorable.

Treatment.

The treatment of purpura is unfortunately most unsatisfactory. In persons who have passed through one attack, recurrences may perhaps be avoided by attention, in the minutest detail, to all of the laws of health. The diet should be carefully regulated, the patient should seek a comfortable home, exposure to cold, overwork, and stimulants must be avoided, and in particular the slightest tendency to bleeding should cause him to take to his bed at once. After the development of the disease the patient must be kept absolutely at rest, as the slightest attempts at movement or at getting up from bed may determine serious hemorrhage. The diet must be light and nutritious and should be altered according to the features of the individual case. Stimulants should be avoided. The administration of mild laxatives is always called for in cases in which there is no tendency to constipation, and even if the bowels are regular it may be advisable to administer gentle laxatives. Sometimes acidulous drinks, particularly such as are made with dilute sulphuric acid, seem to be useful on account of the hemostatic action of the acids employed.

The control of the hemorrhage by medicinal agents is difficult or impossible. Various remedies such as ergot, acetate of lead, peroxide of iron, oil of turpentine, and the like have been employed, but their influence is exceedingly doubtful. None of them should be employed where any danger exists of disturbance of the gastrointestinal tract due to their administration. Perfect rest and compression in case of hemorrhages from exposed surfaces are more efficacious than medicinal agents. Perhaps some of the methods recently suggested for increasing coagulability of the blood, locally or in general, may prove useful in this condition. The administration of chloride of calcium or of other calcium salts should be tried and in a few instances recorded has seemed to be of use. The local application of fibrin ferment in solutions of chloride of calcium (Wright) or of "zymoplastic substances" (Alexander Schmidt) may prove useful. (See Hæmophilia.)

After the cessation of the hemorrhages tonics must be administered and the condition of the blood requires attention. Quinine, nux vomica, and other stomachics together with nutritious diet and life in the open air serve to improve the general condition, while iron and arsenic are useful for the condition of the blood.

Scurvy.

Synonym.—Scorbutus.

Definition.

Scurvy is a subacute or chronic disease occurring in persons of depraved vitality, the result of improper or insufficient diet or of unsanitary surroundings, and marked by characteristic symptoms, including hemorrhages into the skin and deeper tissues, progressive weakness, anæmia and emaciation, and particularly by inflammatory and ulcerative conditions of the gums. Though it is undoubtedly intimately connected with disturbances of nutrition, it is quite probable that the disease is essentially an infection. The micro-organism, however, has not as yet been isolated.

History.

Scurvy has undoubtedly been recognized since the earliest times, though Ling and Hirsch and other systematic writers have been inclined to believe the descriptions given by the older writers to be applicable to other diseases. Notwithstanding the view of these authorities, however, it would seem that the disease was recognized by Hippocrates, and others among the ancients have described affections which may be assumed to have been scorbutic. Pliny in his "Natural History" gives an account of the disease as it occurred among the followers of Germanicus, and Strabo refers to the prevalence in the army of Aellius Gallus of a form of disease having the features of scurvy, though the descriptions are not altogether satisfactory. In the early middle ages scurvy was recognized by Jacques de Vitry among the Crusaders at Damiata; and Joinville in his "History of Louis IX." refers to the occurrence of the disease at Cairo in 1218. During the fifteenth and sixteenth centuries scurvy frequently occurred, though, as Koch observes, the unscientific and for the most part ignorant practitioners of that time have left no descriptions. In later times the disease has been described by Boerhaave, van Swieten, and especially by Lind.

The history of the various expeditions of discovery to America and to northern seas as well as those to India furnish numerous examples of the prevalence of scurvy among seafaring men. It is related that a hundred of one hundred and sixty sailors accompanying Vasco da Gama died when the expeditions was rounding the Cape of Good Hope. The disease has been particularly common, however,

in later times among the mariners in Arctic explorations and until comparatively recent years scurvy has formed one of the greatest obstacles to successful expeditions.

Etiology.

The essential cause of scorbutus is still a matter of much doubt, though the conditions which favor its development are now quite well recognized. It is pre-eminently a disease dependent upon unsanitary surroundings and prevails at the present day in all parts of the world (for instance, Russia, Roumania, and the East) in which sanitary laws are but little observed. In former times it was frequently met with in prisons, in crowded hospitals, asylums, and like institutions in which bad ventilation contributed with other causes to bring about depraved vitality in the inmates. The history of military campaigns furnishes a large chapter in the knowledge of the disease, and among invading armies, but particularly among the people of besieged cities, scurvy has often played sad havoc. Even recently, during the siege of Paris, this disease was one of the most prevalent.

From the earliest times it has been recognized that scurvy may be either endemic or epidemic, though formerly the epidemic prevalence attracted more particular attention. Its occurs in times and in places favoring the conditions mentioned, though occasionally the causes are less conspicuous and less striking. Sporadic cases, however, occur in practically all parts of the world and for the most part local conditions may be found which have been favorable to its development. Thus in large prisons and hospitals, almshouses, and the like a few cases may be found at almost any time.

Geographical Distribution.—No part of the world is free from the disease, though it appears to be more abundant and has always been more prevalent in northern climates and in expeditions in cold countries. It is still quite common in the northern part of Russia, and decided epidemics have occurred in the hospitals of St. Petersburg, Archangel, and other Russian cities in recent years.

The older writers distinguish two forms of the disease—*sea scurvy* and *land scurvy*, and an attempt was made to establish distinctions between the two. This, however, is now recognized to be impossible, since the two diseases are essentially and in every respect the same.

Season.—The season of the year exercises a double influence. Undoubtedly the cold alone bears some relation to the development of the disease; but in addition to this the overcrowding and the lack of ventilation, likely to occur during the colder months or the period of the year when changeable, raw weather occurs, are contributing

causes. The statistics of Hermann establishing the frequency in different months during eighteen successive years at St. Petersburg show that April, May, and June are the months of greatest prevalence, the increase in frequency of the disease from January to May being gradual and progressive, as the decrease from June to December is similarly steady. Amberger found practically the same result in the analysis of the cases occurring in the four large hospitals of St. Petersburg during the years 1871–77.

As there are months during which scurvy is more prevalent, so also statistical evidence shows that the frequency of the disease in different years varies greatly. Sometimes this has been dependent upon unusually rigorous climatic influences, sometimes it has been dependent upon widespread famine or the like. The statistics of Hermann show that the number of cases during 1868 was far in excess of that observed in any other year of the eighteen years covered by his observations, and Amberger's statistics for the hospitals of St. Petersburg, extending from 1867 to 1880, give a similar result.

Conditions Affecting Individuals.—The previous general health has a certain value in the occurrence of scurvy, and in particular overwork, anxiety, and nervous depression of all forms contribute largely to the development of the disease. This is well illustrated in the frequency of the affection among the besieged in cases in which the general hygiene and the diet have suffered but little, while the anxiety and the constant nervous tension have led to general depravity of the nutrition.

Nostalgia is a frequent cause not only among those taking part in expeditions, but also in ordinary life.

Sex.—Sex plays an inferior part in the etiology, although undoubtedly the disease is more common in the male sex than in the female sex under much the same conditions. This was seen in the late siege of Paris and has been frequently observed under similar conditions. It is quite likely, however, that this greater prevalence among the males is dependent upon the overwork and the great anxiety to which men are subjected.

Age.—Scurvy occurs most frequently in adults, though it may be met with in children or in the aged. In institutions for old persons sporadic cases occur from time to time in consequence of bad dentition and carelessness in diet, despite the fact that the surroundings may be satisfactory in every respect (Henry).

In recent years attention has been called to the frequency of scorbutus in infants, and numerous cases have been reported in England, America, and on the Continent of Europe. This, however, will be considered in a separate section.

Predisposition.—Certain diseases such as malaria, syphilis, and dysentery seem to predispose to the development of scurvy, as may other conditions which lower the general vitality. Among these gastrointestinal disorders, defective dentition, and alcoholism play an important part. Occasionally there seems to be an hereditary tendency to the development of the disease, though it is difficult to determine how far this is only apparent and in reality due to similarity of surroundings, diet, etc.

Diet.—The most important condition, however, among the etiological factors in the development of scurvy is diet, to which attention has always been called by those who have investigated the disease. An immense amount of ingenious study and speculation has been devoted to this question and the opinions have varied almost as greatly as the investigators themselves. At different times it has been held that the use of salted meats, of improperly prepared foods, partly decomposed meat, fish, or vegetables, of an insufficiency of vegetable food, of excess of fatty food, or of a too monotonous diet in general is the essential cause.

At the present time it must be conceded that improper diet is the most important cause of the disease, but it is most likely that the transgression in diet may occur in different directions. Any departure from the normal relation of carbohydrates, of proteids, and fats continued for a long time, or a general deficiency of diet may lead to the development of the disease. Sometimes it has been found that one of these essential forms of food has been deficient, sometimes it has been another. Improper preparation of the food may be just as potent as departure from the normal proportions. The theory which has gained the greatest number of adherents is that which has ascribed the development of the disease to the lack of fresh vegetables, and this theory receives a considerable amount of support from the repeated observations that a resumption of vegetable diet quickly dispels the symptoms of the disease and that the disease is particularly prevalent in some sections among persons who habitually neglect vegetable diet, as is the case with the bush-rangers of Australia. While there is no doubt of the importance of these facts, it is nevertheless true that scurvy may occur in persons who partake of the usual quantity of vegetable food, but whose diet is of a monotonous character or ill prepared. In children, according to Ingerslev and Cheadle, the constant use of carbohydrates is regarded as important, while others have found that the overheating of milk in the process of sterilization or the continuous use of a milk of poor quality has been the direct cause.

Another cause of importance is the constant use of bad drinking-

water, and it has been repeatedly observed that the disease ceased in armies or garrisons, in which it had been prevalent, after a change in the water-supply and without any other regulation.

Pathogenesis.

Various views have been entertained regarding the pathogenesis of the disease, and theories having more or less probability have been constructed. These have for the most part owed their origin to the general belief that scurvy is the result of errors in diet and in particular to the view that abstinence from certain foods and exclusive consumption of other kinds are the essential causes.

One of the theories referred to sought to explain the disease upon the assumption that it results from excess of sodium chloride in the blood and other fluids of the body. Some probability was lent to this opinion by the frequent occurrence of scurvy among sailors whose diet was almost wholly composed of salted meats, and still more by the chemical examinations of the blood, showing excess of chloride of sodium. As for the excessive consumption of salt, it has now been proved that this is by no means essential to the production of the disease; and the importance of the second point (the excess of NaCl in the blood) has been wholly removed by the uniform discovery of the same condition in all forms of anæmia.

The theory which has gained the greatest popularity is that of Garrod, who maintained that the disease results from a diminution of potassium in the blood and tissues. The occurrence of the disease in persons abstaining from diet (vegetables) rich in potassium, the relative increase of potassium in the urine, and the fact that the blood in scurvy shows diminution in the amount of this substance, all gave a certain amount of likelihood to the theory. A searching examination of the facts, however, renders the view of Garrod improbable in the light of modern investigation. Absence or diminution of potassium in the diet is by no means requisite to the occurrence of the disease, and the excess of potassium in the urine is relative, not absolute. As for the reduction of the potassium in the blood, this is now recognized as a constant condition in all forms of secondary or symptomatic anæmia, and is therefore of no particular significance. There is no proof to support the view that the body, as a whole, suffers any poverty of potassium.

Another chemical theory that must be considered as having suffered the fate of those just mentioned is that maintained by Ralfe and others who hold that the lack of malates, citrates, and lactates in the diet leads to a reduction of the normal alkalinity of

the blood, to which the conversion of these salts into carbonates largely contributes.

Infection.—Considerable evidence may be adduced in favor of the view that scurvy is an infectious disease, though the absolute proof of such a view remains to be furnished. Reference has already been made to the fact that the disease occurs in epidemic form. In such instances it is quite likely that the surrounding conditions to which considerable numbers of people are subjected, may furnish the explanation of the simultaneous occurrence of the disease in different individuals. This does not, however, exclude the activity of a specific organism for which insanitary surroundings prepare the way. The question would be practically settled if any instance of direct contagion could be cited; but such an occurrence has never been proved, and the probability or improbability of the infectious nature of the disease must rest upon the consideration of its course and pathological features, and upon certain more or less convincing experimental and bacteriological studies. Undoubtedly the clinical features of the disease and in particular the purpuric and other hemorrhages do give the infectious theory a certain amount of credibility, as do also the generalized character of the lesions and the nature of some of the lesions in themselves. More striking evidence was furnished by the experiments of Murri, Cantu, Pari, and Petrone, who injected the blood of scorbutic patients into animals and noted the development of purpuric lesions. These symptoms, however, cannot be positively asserted to have been evidences of scurvy in the animals upon which the experiments were performed, and may be looked upon, as some have held, rather as signs of ordinary septicæmia. Several observers, as Kamen, Rosenell, and Uskow, found micro-organisms in the blood or in the organs and were inclined to regard these as specific. On the other hand Wierinzski failed to find bacteria in the blood and believed that the disease is essentially a toxæmia resulting from the absorption of poisonous substances from the gastrointestinal tract, such toxic agents being products of micro-organisms in the intestinal contents. The most active supporter of the infectious theory is Babes who has recently (1893) contributed interesting studies of the disease. In examining the blood in a number of cases, and excised portions of the gums in two, he was able to demonstrate the streptococcus and a peculiar bacillus of long and slender shape. These bacilli were found in the superficial as well as the deeper tissue of the gums, though in the former situation they were partly degenerated (granular). Parts of the tissue of the gums were rubbed up and injected into the circulation of two rabbits, causing death in from six to eight days. In one, there were hemorrhages

in the subcutaneous tissues and in the serous membranes; in the second, ecchymoses in the muscles, liver, and intestines as well. Histological examination of the organs of the rabbit showed bacteria in the capillaries of the lungs and in the pulmonary alveoli and in the spleen, and hemorrhagic infiltrations in the liver. The bacilli found in the gums were obtained in pure culture and injected into animals, causing death in from six to ten days. In the bodies of the dead animals hemorrhages were found in the subcutaneous tissues and in the serous membranes. The author concluded that the organism in question, which was previously described by Müller, though never cultivated, is a frequent parasite of the mouth, though special conditions are required to favor its multiplication and activity. He ascribes to it the power of causing necrosis of the gums and secondarily through the production of toxic substances the development of proliferative changes in the fixed connective tissues and in the walls of the blood-vessels.

In recapitulation it may be said that a careful review of the evidence warrants a strong suspicion that scurvy is an infectious disease, though the positive proof is lacking and the bacteriological examinations are upon the whole unsatisfactory. Even though the disease should be proved to be infectious, however, it would remain quite certain that insanitary surroundings and improper diet are factors of the greatest importance in preparing a suitable soil for the occurrence of scurvy.

Morbid Anatomy.

The anatomical changes discovered post mortem are often widespread and striking, though for the most part not characteristic. The surface of the body may present numerous dark-colored ecchymotic points or areas of reddish, bluish, brown, or green color according to the age of the individual lesion. Extreme emaciation may be noted and sometimes the subcutaneous tissues about the ankles or legs and the other loose cellular tissues are swollen by œdema. Rigor mortis is generally poorly marked and rapid post-mortem decomposition has sometimes been noted. On section into the superficial tissues and muscles more or less extensive hemorrhagic foci are discovered, particularly in the muscles of the calf, the buttocks, and about the flexures of the joints. The blood may be entirely fluid, or partial coagulation may be observed; very rarely degenerative changes or actual suppuration may be noted. More frequently a tendency to fibrous proliferation occurs, and the hæmatomata may be surrounded by thickened connective tissue and may be partly organized.

Serous effusions are not infrequently present in the joints, and the synovial membranes are congested or marked by ecchymoses. The liquid in the joints may sometimes be hemorrhagic in character and very rarely purulent arthritis is observed. Pseudoankylosis due to the formation of fibrous tissues about the hemorrhagic extravasations in the vicinity of the joint is not infrequent.

The internal organs may be pale in consequence of the general anæmia, but this is rarely a striking feature. The serous surfaces (pericardium, pleura, meninges) like the joints are often congested or present ecchymoses of greater or less extent. Serous effusions are extremely frequent and large collections of liquid may occur in the pleura or pericardium. The peritoneum is less commonly involved. The effusion in the pleural sacs and less frequently that in the pericardium may be distinctly hemorrhagic. Actual inflammatory changes of the serous surfaces are rarely striking, though a distinct pleuritis is occasionally seen.

The lungs are frequently œdematous and small hemorrhagic foci or irregular areas of infiltration are quite common. Submucous hemorrhages are seen in the larger bronchi and sometimes extend throughout the entire bronchial system. The fatal result in scurvy is not rarely due to the development of scattered areas of bronchopneumonia or to extensive lobar pneumonia.

The heart is soft and light in color, presenting more or less advanced parenchymatous or fatty degeneration, and ecchymoses may be found beneath the epicardium or endocardium. Marantic thrombi are found within the cavities in cases in which death has been slow, but they are rarely well formed. The cardiac chambers may be considerably dilated in consequence of the degeneration of the myocardium, and relative incompetency of the valves may be thus occasioned. Acute endocarditis is sometimes seen, although it is not a frequent lesion.

The gastrointestinal tract is nearly always affected in some part. The lesion which is most nearly specific is that involving the gums and buccal mucous membranes. The tissue of the gums becomes reddened and swollen and in the later stages undergoes varying degrees of necrosis with coincident proliferation of the connective tissues, leading to the formation of distinct fleshy protuberances. The surface epithelium may remain intact, but more commonly about the edges of the gums adjoining the teeth erosion or extensive ulceration is noted. Microscopically the superficial portions of the gums present quite advanced degeneration, while the deeper layers show a great degree of proliferation of the fibrous connective tissues. Small hemorrhages are usually seen, and the blood-vessels of the gums

have been found to present proliferations of the endothelium in some parts, leading to obstruction of the lumen of the vessel and consequently overdistention of the vessel and separation of the endothelial cells on the proximal side of the obstruction (Uskow, Swiderski). The lesions of the gums most frequently begin about the incisor teeth and may be particularly pronounced in the portions of the gums between the teeth. Later the process extends to the gums surrounding the bicuspid and molar teeth, while the lips and mucosa covering the cheeks are rarely involved. Acute inflammatory processes have been observed about the pillars of the fauces and in the pharynx; and hemorrhagic extravasations may occur in any part of the mouth, though they are most frequent in the gums.

The stomach and intestines frequently present hemorrhagic suffusions in the mucous membrane or submucous tissue, and erosions or follicular ulcers are not unusual. Extensive ulceration, however, is rare.

The liver is frequently fatty and in cases marked by considerable anæmia may be decidedly pallid. Small hemorrhages are not unusual. The kidneys rarely present decided lesions. Ecchymoses may be observed beneath the mucous membrane of the pelvis and in one of my cases a considerable extravasation of blood occurred in this situation. Similar hemorrhages may be observed in the substance of the kidneys and sometimes nephritis occurs as a complication.

The blood-making organs frequently show some alterations, though these are in no wise specific. The spleen is enlarged in a notable proportion of the cases, and sometimes becomes of considerable size. The substance of the organ is dark in color and rather soft, and small hemorrhagic infarcts are not unusual. The lymphatic glands are less commonly involved, though the mesenteric nodes are sometimes increased in size and may present hemorrhagic infiltration. A lymphoid condition of the bone marrow has been observed by Uskow and by others, while punctate or diffuse hemorrhagic infiltration of the marrow substance is not unusual in severe cases.

The bones may present fractures or caries, and separation of the epiphyses has been described by a number of observers.

The Blood.—The condition of the blood in scurvy presents no characteristic features. The chemical examination was regarded by the older writers as of great importance, but modern investigation has shown that the changes observed are characteristic of anæmia in general rather than of a particular disease. Considerable weight was given by those who adhered to the theory of Garrod to the discovery that the potassium of the blood is decreased in quantity, while

others insisted upon the importance of the increased quantity of sodium chloride. Recent studies, however, show that both of these conditions occur in most of the symptomatic anæmias, and Albertoni in particular has demonstrated that the variation from the normal amount of potassium and sodium in scorbutic blood is no greater than that observed in other anæmias. The alkalinity of the blood has been found decreased by some, while others have found it increased. It is likely that decreased alkalinity is the prevailing condition, but the explanation of Ralfe that this is dependent upon decreased consumption of vegetable salts convertible into carbonates is erroneous.

The number of the red corpuscles is usually but moderately decreased. In ordinary cases the number is found to be from 4,000,000 to 3,000,000 per cubic millimetre; in severe cases the number may fall to 2,000,000 or 1,000,000, especially when extensive hemorrhages have occurred. In instances in which extreme hemorrhages have taken place the reduction in the number of red corpuscles may be excessive, Bouchut having recorded one in which they numbered but 557,875 per cubic millimetre. In cases in which the anæmia is decided, the individual erythrocytes usually present some alterations from the normal, such as irregularity in the size or moderate poikilocytosis and polychromatophilia. These changes, however, are rarely striking, excepting in cases marked by severe hemorrhages. Under such circumstances the appearance of the blood may be that of the most extreme anæmias, and microcytes and nucleated red cells may be abundant. The hæmoglobin is decreased in quantity, and it has been frequently noted that its reduction is more marked than is that of the red corpuscles. This disproportion is usually slight, but at times becomes marked enough to give the blood the characteristics of the chlorotic condition.

The white corpuscles may be entirely normal in number and in appearance. Very commonly, however, there is a moderate leucocytosis, the number of leucocytes per cubic millimetre ranging from 15,000 to 40,000, such increase in the number of leucocytes being, of course, most frequent in instances in which there has been considerable hemorrhage.

The blood plaques have been found increased by some observers, and Penzoldt has called attention to the occurrence of abundant small bodies, some of them granular and some of them highly refractive, which suggested undeveloped erythrocytes.

Symptoms.

The onset of scurvy is rarely sudden and is usually preceded by certain prodromes such as increasing weakness, gastrointestinal dis-

turbances, and pallor. Occasionally the disease is ushered in with local inflammatory troubles, such as sore throat, or the first manifestation may be a severe hemorrhage. Nyctalopia or night blindness and hemeralopia have been noted, particularly among mariners, as prodromes or as symptoms of the fully developed disease.

After the condition has been well established the appearance of the patient is quite characteristic. The skin becomes pale or more frequently assumes a somewhat earthy hue, increasing with the increasing severity of the affection. Occasionally the skin and the conjunctivæ present a moderate icteric hue in addition to the pallor, while lividity or cyanosis of the lips and of the extremities may sometimes be marked. The surface is dry and the epidermis may present scaly desquamation. The features are pinched, the eyes sink deeply into the orbits, and dark rings about the eyes add to the striking facies of the disease.

The patient's general condition is one of extreme depression, the strength failing progressively until he is entirely prostrated and confined to bed. He becomes morose or melancholic or sometimes exceedingly irritable, and every attempt at exertion may determine severe attacks of dyspnœa or of palpitation. The appetite may cease entirely or, on the other hand, there may be abnormal craving for food.

The Gums.—The most striking objective manifestation is that observed in the gums. This may occur soon after the onset of the prodromal symptoms, or it may be late in development. In old persons who have lost their teeth and in infants before dentition the mucous membrane of the mouth is frequently entirely healthy, though ulcers may occur even in such instances. The changes begin in the gums surrounding the incisor teeth, and subsequently spread to the other parts. The earliest change noted is a red line of congestion immediately around the neck of the tooth, which gradually spreads until the entire gum is congested and swollen. Subsequently the tissue becomes œdematous and necrotic, projecting as a soft or mushy and friable tissue, and bleeding on the slightest touch. Sometimes the swelling is so marked that the teeth are completely hidden from view and in the severest cases the surface of the gums may be covered by a dirty pseudomembrane. Hemorrhagic infiltrations are prone to occur and considerable hemorrhages from the mouth are not unusual. The patient complains of constant discomfort and of severe pain whenever he attempts to eat. The saliva is usually increased in quantity, and with the admixture of blood from the bleeding gums may dribble from the mouth as a sanious liquid.

The tongue is coated and the breath is generally horribly fetid.

As the condition of the patient improves the lesions of the gums become less marked and ulceration may occur without notable alterations of the tissue. In other cases considerable loss of substance occurs and dense scar tissue may take its place. In cases progressing unfavorably the necrotic processes of the gums may increase until the roots of the teeth are laid bare and actual dislodgment of the teeth sometimes occurs.

Next in importance to the condition of the mouth are the *hemorrhagic manifestations* of the disease, the latter usually occurring after the changes in the gums have begun. The most frequent situation of hemorrhages is the skin of the legs near the ankle and as a rule both sides are simultaneously involved. The lesions present themselves as small punctate ecchymoses which may grow somewhat in size and coalesce, and change from a bright red color to a darker red, then to a brown and yellow or green, the changes of color being similar to those seen in ordinary bruises. After the legs other parts of the body may be involved, but ecchymoses are rarely seen upon the face. Blows or the pressure of clothing and other external causes may determine the situation of the hemorrhages and may lead to considerable extravasations. Careful examination shows that the hemorrhages are perifollicular and periglandular, occurring about the hair follicles or the sweat glands. As a rule there is but little elevation above the surface, though occasionally the hemorrhagic infiltration is sufficient to produce slight papules (*acne scorbutica*). The skin covering the hemorrhagic area, as a rule, remains intact, but occasionally it forms vesicles or blebs (*herpes seu pemphigus scorbuticus*) and extensive ulcers may occur. The latter sometimes remain as indolent sores and may be covered with a considerable deposit of dried crust (*rupia scorbutica*).

Subcutaneous and Intermuscular Hemorrhages.—More extensive effusions of blood occur beneath the skin involving the subcutaneous cellular tissue, the intermuscular septa, and the fibrous tissues surrounding the joints. These may be diffuse and infiltrating in character, or may constitute actual hæmatomata. Hemorrhages in the muscles themselves are less frequently observed. The skin over the affected parts may be firmly attached, though this does not usually occur in marked degree. Palpation reveals more or less superficial or deeply seated doughy masses, and the temperature in the affected part may be slightly elevated. The skin is usually somewhat fixed, though in the earlier stages, at least, it appears to take no part in the processes. In the later stages discoloration may occur and may suggest the extravasation of liquid from a hemorrhagic area. Inflammatory changes may lead to increased swelling and the area may under-

go extensive necrosis, discharging partly clotted blood and shreds of tissue and leaving a more or less indolent ulcer. In more favorable cases the extravasated blood is gradually absorbed and the tissues return to the normal condition; but not rarely overgrowth of fibrous tissue occurs and leads to sclerotic areas between the muscles or beneath the skin, and when the lesions surround the joints pseudo-ankylosis may be developed.

Subperiosteal hemorrhages are observed in the scurvy of infants with extreme frequency, while hemorrhages about the nerve trunks are occasionally seen.

Bleeding from the mucous membranes constitutes one of the frequent and more serious manifestations of the disease. Hemorrhage from the mouth is perhaps the most common, but epistaxis, hæmatemesis, hemorrhage from the bowels, uterus, or lungs, and hæmaturia have all been noted. Such hemorrhages may be early or late manifestations and may occur with great suddenness, or after a period of moderate bleeding.

Swelling of the joints occurs in scurvy as in all of the hemorrhagic diseases, but is rarely marked. The knee and ankle joints are most frequently involved. Signs of effusion and of local inflammatory reaction may be discovered and in occasional instances actual suppurative arthritis is developed.

Fever is prone to occur from time to time in an irregular form but may be entirely absent. Not rarely its presence is explained by the discovery of some complication such as pleurisy, pericarditis, or subcutaneous abscess formation.

The gastrointestinal symptoms are frequently striking and may completely overshadow the other symptoms of the disease. As has already been pointed out, the appetite sometimes fails entirely and at other times assumes a voracious character, the patient in the latter instances, as a rule, showing a decided preference for sour foods and condiments. The digestion is commonly disturbed and vomiting may be a distressing symptom. The bowels are usually constipated and may be obstinately so. Attention has frequently been called to the occurrence of attacks of diarrhœa of dysenteric character and the term *scorbutic dysentery* has sometimes been applied. In such instances the dejections are hemorrhagic in character and contain variable quantities of mucus, but are usually much more abundant and much more watery than the stools of ordinary dysentery.

Circulatory disturbances and disorders of the *respiratory* system are prone to develop in proportion to the degree of anæmia and of the general weakness. The pulse is rapid and weak and in the later stages or after hemorrhages may become extremely feeble. Physi-

cal examination of the heart not rarely discovers some enlargement of the organ, and murmurs may be met with at the base of the heart or in the vessels of the neck. Organic lesions and murmurs of valvular incompetency are unusual. The respirations are hurried and the inspiratory efforts increasingly feeble. Severe attacks of dyspnœa may occur from exertion or in consequence of emotional disturbances. Slight cough without expectoration is common and acute bronchitis is frequently noted and may be attended by increased cough and by expectoration.

The *urine* shows no decided changes. The quantity is sometimes reduced, in other cases it is normal or even excessive. The reaction is usually acid, though less markedly than in the normal urine, and a tendency to alkaline fermentation is frequently noted. Chemical examination shows a diminution in the quantity of urea and of the saline constituents, with, however, a relative increase in the amount of potassium. Albumin is frequently observed, though casts and other evidences of nephritis are unusual. Grocco reported the discovery of peptonuria. The nature of the albuminous substances in this case, however, must be doubted.

Nervous symptoms may sometimes become prominent. Ordinary cases are marked by depression and languor. In severe cases there may be delirium and even deep coma, and epileptiform convulsions have sometimes been observed. These more violent manifestations, as a rule, are dependent upon hemorrhage into the membranes of the brain.

The *eyes* present a striking appearance, as has already been noted, being deeply sunken and surrounded by dark rings. Hemorrhages may occur into the conjunctiva, in the anterior chamber, in the choroid, or in the retina. In such cases vision may or may not be disturbed. Ophthalmoscopic examination shows punctate or linear extravasations of blood of bright red color in the earlier stages and tending to become more and more yellow in the later stages. Hemeralopia and nyctalopia are occasionally symptoms of the disease.

Clinical Course.

The course of ordinary cases is subacute or chronic, lasting from three or four weeks to as many months; relapses are frequent and may lead to extreme chronicity. In very rare cases the onset of the disease is violent and abrupt and the duration is short. In such instances the first manifestation may be a severe hemorrhage occurring in a person previously entirely well, or one who had manifested only vague prodromal symptoms. A sudden hemorrhage or an attack of

hemorrhagic diarrhœa may at once lead to a grave condition from which the patient does not recover.

In ordinary cases the onset is slow and the course of the disease is progressive, though marked by considerable fluctuations from time to time. Death may occur from gradually increasing weakness and inanition, from the development of large serous effusions, œdema of the lungs, or pneumonia. Occasionally the fatal termination is due to sepsis resulting from secondary infections, and a rapid termination may be due to hemorrhage.

Complications and Sequelæ.

Scurvy is marked by numerous complications, some of which have already been alluded to. One of the most frequent and unfavorable is pneumonia, this being either of a lobular form or a frank croupous pneumonia. These conditions may run their customary course and terminate favorably; but they frequently prove fatal, or in other cases resolution is protracted and gangrene of the lungs may ensue. Large pleural effusions of sanguinolent type are met with in a considerable proportion of cases in which the general vitality has been greatly reduced, and œdema of the lung is frequently developed in the later stages of the disease. Gastrointestinal complications of various kinds may interrupt the course of the disease, or may lead to its final termination. Among the less serious are pharyngeal ulceration, protracted vomiting, and other gastric disturbances; of the more serious, diarrhœa of dysenteric character is the most frequent. Cardiac complications such as acute pericarditis and acute endocarditis are occasionally met with, and inflammatory lesions of the other serous surfaces may be observed.

Various sequelæ may result from the alterations which take place in and about the subcutaneous or deeper hemorrhages. The most important of such sequels is ankylosis of the joint, this being especially frequent about the knee, elbow, and ankle joints. Considerable deformity may be brought about in this way.

Diagnosis.

The diagnosis of scurvy presents a number of difficulties. In the first place it must be noted that many of the cases of atypical form occurring in persons in whom the disease would not be ordinarily suspected are overlooked. According to Hammond and Woodward a great many of the cases in our late Civil War were classified as instances of "general debility" and the like. The diagnosis is particu-

larly apt to be difficult when the disease occurs in persons whose surroundings are entirely favorable, as in one instance which came under my observation in a man of considerable wealth, in whom the first manifestations were abrupt and violent, and in whom there had been no premonitory evidences of the disease at all. The subsequent progress of the case, however, made the diagnosis comparatively easy.

The symptoms which are most significant are the subcutaneous and particularly the deep-seated hemorrhages, the ecchymoses upon the skin, and the alterations found in the gums. It must, however, be remembered that the changes in the gums are absent in old persons who have lost their teeth as well as in young children. The result of treatment also aids in the diagnosis.

When in addition to the symptoms noted the surroundings of the patient are such that scurvy might reasonably be expected the diagnosis is quite certain. Scurvy differs from the purpuric affections in the absence in the latter of specific alterations in the gums and in the absence of the deeper-seated hemorrhages. The joint manifestations are prone to be more severe in purpura, while the hemorrhages and other changes surrounding the joints are less marked.

Scorbutic pleurisy, pericarditis, and similar conditions may be recognized by the discovery of the specific lesions in the mouth or by the discovery of deep-seated hemorrhages in cases in which superficial ecchymoses are entirely absent.

Prognosis.

The prognosis is ordinarily favorable, provided the patient can be placed under suitable conditions. In cases, however, in which the disease has become firmly established and particularly in epidemics the affection is one of great gravity. The disease usually continues for several weeks under the most favorable circumstances and may be protracted for months or even years.

Treatment.

The prophylaxis comprehends attention to every detail of daily life and diet. The surroundings of the patient, even though favorable, should be changed. Sometimes sea air and sometimes mountain climates prove most beneficial; and in any case a change is desirable.

If the patient has been greatly reduced by the disease absolute rest should be enjoined for a time, and subsequently the return to

daily activity should be gradual and under strict regulation. The patient should be as much as possible in the open air, or, when the weather does not permit of this, free ventilation of the apartments must be insisted upon. The regulation of the diet in scurvy is one of the most important parts of the treatment. Various food stuffs have become noted as antiscorbutic in character. Among these fresh vegetables and particularly potatoes, lettuce, spinach, sorrel, and fruits have been highly recommended. Whether this antagonistic character actually does belong to such foods or not, it is certain that an abundance of fresh vegetables and meat, and in general a wholesome mixed diet is most important in the treatment of the disease. A reliance upon any one or other of the so-called antiscorbutic foods would be most fallacious. Fresh fruits or fruit juice, and particularly apples, lemons, and oranges and lime juice are most efficient adjuvants. Scurvy rarely develops in persons using a diet of this character. Occasionally, however, the disease occurs despite the diet and is then attributable to other conditions which prevent proper assimilation of the food taken. The importance of diet as a prophylactic measure is well illustrated by the practical extermination of this disease among mariners, and the law of most nations requires that lime or lemon juice, vinegar, and sugar shall be carried in sailing-vessels bound on ocean voyages or engaged in fishing.

Among the drugs which have been commended as antiscorbutics the vegetable salts of potassium have obtained the widest popularity, largely in consequence of the views of Garrod and his followers. Whether they actually exercise antiscorbutic power or not, they may be useful in regulating the condition of the gastrointestinal tract and in stimulating free secretion.

When anæmia is marked, the treatment should be directed to improving this condition. Iron may be used in the form of Blaud's pill or in some other of its non-constipating preparations. Arsenic, however, is more valuable and should be given continuously until the patient has regained his usual health.

Transfusion has been practised in some cases after severe hemorrhages when the anæmia has been intense, but there is no evidence to show that it exercises any decided influence. Hypodermic infiltrations with saline solution are doubtless quite as efficient in combating sudden anæmia.

Attention must always be paid to the state of the gastrointestinal tract. The condition of the mouth demands the greatest care both in the well-developed disease and in the earlier stages, or as a preventive measure. Undoubtedly improper care of the teeth greatly favors the development of the disease and the use of antiseptic mouth-

washes and particularly of chloride of potassium is valuable as a measure of prophylaxis. After the development of the disease the same care should be continued, and in case of ulcerations of the gums applications of solutions of nitrate of silver should be made directly to the diseased surface. Stomachic tonics, such as cinchona, gentian, or nux vomica, are particularly advisable in cases in which the appetite is deficient and the process of digestion is retarded. Dilute hydrochloric acid may be combined with these remedies and administered after meals with considerable advantage to the digestion.

Constipation must be avoided by the regulation of the diet and the administration of salines. Care should be taken, however, to avoid excessive purgation, as intestinal irritation may lead to the development of diarrhœa which tends to assume the dysenteric type and leads to rapid constitutional depression. In cases in which diarrhœa occurs astringents, such as the aromatic sulphuric acid, quassia, or hæmatoxylon, should be administered and the diet should be strictly regulated.

The hemorrhages cannot be controlled directly. Rest in bed should be secured and hæmostatic remedies, such as ergot, dilute sulphuric acid, oil of turpentine, or gallic acid, may be administered, though the value of these remedies is extremely doubtful. Calcium salts may prove useful in rendering the blood more coagulable.

During convalescence the patient should continue the use of general tonic remedies, such as arsenic, iron, quinine, and nux vomica; he should take daily exercise in the open air and continue a liberal mixed diet. Hydrotherapeutic measures also prove valuable, particularly cold affusions followed by vigorous friction.

Scurvy in Infancy.

Definition.

Within recent years a form of disease has been recognized in young children which has been regarded by some as a form of acute rickets, but is now quite generally known to be scurvy. It is characterized by a tendency to subperiosteal hemorrhages, particularly in the lower extremities, pseudoparalysis, and a general cachectic condition.

History.

The first case of this description seems to have been recognized in 1875 by Ingerslev who reported a case and called attention to the scorbutic nature of the disease. In 1881 five cases were described by Gee under the title of "osseous and periosteal cachexia." In 1878,

Cheadle reported three cases with marked lesions of the gums, while in 1879 and 1882 the same author reported further instances and insisted that the disease was the outcome of a rachitic diathesis. The most accurate descriptions of the affection, however, are those published by Barlow in 1883 and 1895.

Etiology.

The frequency of infantile scurvy cannot as yet be accurately determined. Undoubtedly the disease is more often overlooked than recognized, and the cases which have been hitherto described have occurred in the practice of pædiatric specialists. The body of the profession seems as yet to have recognized the disease but rarely, and as it occurs more frequently in private practice than in hospitals its frequency cannot well be estimated.

The infantile form of scurvy, unlike that of adults, occurs more frequently among the affluent than among the poor. The explanation of this apparently paradoxical fact is found in the observation of Cheadle that the almost universal habit among the poor of giving young infants some of the ordinary table food of the adults prevents the monotony of diet, and particularly the lack of carbohydrate food which leads to the disease in the children of those more favored.

Age.—It is more common in children between the age of six months and a year and a half than at other periods. It is extremely rare in infants less than four months old, no cases younger than this having occurred in the experience of Barlow, Rotch, Northrop and Crandall, or Southerland. Occasionally it is met with in young children from two to six years of age.

Diet.—Undoubtedly the immediate cause of infantile scurvy is improper diet. The disease has been found among children fed with an unvarying diet of sterilized milk, condensed milk, or some form of prepared food, and it is likely that the monotony of the diet is more important in the causation than is the character of the food.

Some writers have insisted that the cooking of the milk in the process of sterilization is an important cause of the disease (Heubner, Barlow), but others as decidedly dissent from this view (Rotch).

Rickets, syphilis, and other general diseases have been supposed to bear a close relation to the disease under consideration. Particularly has this been true of rickets, many authorities, especially the Germans, holding that it is essentially a form of acute rachitis. Undoubtedly there is some connection, the two diseases occurring under similar circumstances and often coinciding in the same individual; but in many cases of infantile scurvy there are no evidences of rickets,

while in others in which the diseases are coincident treatment removes the scorbutic symptoms, leaving the rachitic manifestations uninfluenced. These facts were well illustrated in Barlow's series of cases, and in the sixty or seventy occurring in the practice of Rotch only about a dozen showed any evidence of rickets.

The supposed relationship of syphilis is still more doubtful or remote. In the majority of instances the history gives no indication of this disease, and in the cases in which such history is obtainable the conditions are merely coincidental. A certain superficial resemblance to rheumatism is presented in infantile scurvy and this has suggested an etiological relationship to some observers. There is, however, no actual connection, as the affection of the joints is only an apparent one, and cardiac complications and similar rheumatic manifestations are entirely wanting.

Pathological Anatomy.

The important lesions of the disease are the hemorrhages. There may be small petechial extravasations in the skin of the legs, particularly in the parts overlying the more deeply situated hemorrhages; but these are not often striking manifestations. The important and significant hemorrhages are those which occur in the subperiosteal tissues. The most frequent situation is the lower part of the femur; next in frequency is the periosteum of the tibia; but the arm bones, the scapula, and the orbits are not rarely affected. The hemorrhagic collections surrounding the orbits, while comparatively infrequent, give rise to a quite striking and characteristic condition, namely, the protrusion of the globe of the eye called proptosis.

The superficial layers of the bones adjacent to the periosteal hemorrhages frequently present some evidences of necrosis; and fractures of the bones are not uncommon. The joints are generally but little involved, though occasionally some effusion may occur in the synovial sacs. More frequently hemorrhagic collections surround the joint and lead to superficial appearances of disease of the joints themselves.

Hemorrhages may occur in the internal organs, notably the lungs, spleen, kidneys, and intestinal glands.

The gums, as a rule, present no change at all before the eruption of the teeth, though occasionally redness and slight erosion may occur, and considerable swelling and ulceration may be observed in the gum covering a tooth prepared for eruption. After the appearance of the teeth the scorbutic manifestations in the gums resemble those seen in adults, though they are less decided in character. Hemor-

rhage from the mouth occurs in such cases as in the scurvy of later life.

The blood shows no characteristic alterations, but the number of red blood corpuscles is more or less reduced, according to the severity of the disease. In ordinary cases the number per cubic millimetre is from 2,000,000 to 3,000,000; in severe cases it falls much lower. The white corpuscles present no striking alterations, though in three cases recorded by Rotch the mononuclear elements were much increased at the expense of the polymorphous forms.

Symptoms.

The disease begins very gradually as a slowly developing cachexia and with apparently no direct exciting cause. The child grows restless and peevish, lying perfectly quiet when left alone, but crying and struggling as soon as touched. The skin grows more and more pale and when the disease is well developed assumes a somewhat ashen or earthy hue. At the same time evidences of subacute gastrointestinal disturbances make themselves apparent, though these are rarely conspicuous. The abdomen is usually somewhat swollen, and regurgitation of the food may frequently be observed. The appetite decreases so that the child nurses badly or, on the other hand, there may be an excessive craving after food. Diarrhœa is frequently present and the stools may contain yellow or greenish curds.

The most characteristic symptoms of the disease are hemorrhages beneath the peritoneum. These affect the long bones and particularly the femur and the tibia, though the bones of the forearm, the scapula, and other bones may be affected. Usually both sides of the body are symmetrically involved, although this is not always the case. Peculiar pyriform swellings are observed surrounding the diaphyses of the bones, beginning at the epiphyseal junction and gradually decreasing towards the shaft of the bone; and on palpation the swellings are found to be somewhat boggy, though the skin is tensely distended. The child lies with the legs flexed upon the thighs and the thighs upon the abdomen in the earlier stages, and cries and shows other evidences of pain whenever the affected parts are touched or moved. The temperature of the affected part may be somewhat elevated; usually this is not the case.

In the later stages the legs instead of being drawn up are extended and the toes usually turn outwards. The reflexes (knee and plantar) are usually preserved, but the leg lies helpless and the term *pseudoparalysis* given to this condition is therefore eminently appropriate.

In the skin over the affected parts small petechial ecchymoses may make their appearance or darker colored, bluish macules may present themselves and give the impression of extravasation of the blood from beneath. Occasionally petechiæ are noted in the skin of other parts of the body, though the hemorrhages are rarely severe or striking. Extravasations of blood about the orbits press the globe of the eye forward, giving rise to the peculiar appearance known as proptosis. At the same time it may be noted also that the eyelids themselves are œdematous.

Hemorrhages from the bowels may occur but are unusual; in some instances hæmaturia has been noted (Gee and Thompson). The condition of the mouth is interesting in connection with the disease as it occurs in adults. In the cases occurring in younger children in whom the teeth have not as yet appeared, the mouth may be entirely healthy, though a certain amount of redness is sometimes seen. In the cases occurring later, swelling, congestion, and finally ulceration or necrosis of the gums surrounding the teeth is quite common and extensive ulcerations may occupy the mouth. The tongue is frequently dry and coated, and the breath is fetid as in the disease occurring in adults.

In some cases examination of the bones detects crepitation, and fractures at the lower end of the femur and the upper end of the tibia or less commonly elsewhere are not infrequent. According to Barlow, the sternum and the costal cartilages tend to sink in and enlargements may be observed about the bones of the head and face.

The joints are little involved; the apparent swelling of the articulations being in reality due to the infiltration and swelling of the tisues surrounding these structures.

The course of infantile scurvy tends to be more or less progressive, though marked by fluctuations as long as the improper diet is continued.

Diagnosis.

The recognition of infantile scurvy is usually made without difficulty when the features of the disease are kept in mind. The most characteristic conditions are the peculiar pyriform swellings of the epiphyseal ends of the bones, the spastic or contracted condition of the limbs in the earlier stages and the pseudoparalysis of the more advanced periods of the disease, the extreme pain and the occurrence of ulcers in the mouth in cases in which the teeth have made their appearance. Œdema of the eyelids has been considered characteristic by some clinicians.

The differential diagnosis between rickets and infantile scurvy is

rarely difficult. The latter disease presents no evidences of a rachitic rosary or the other rachitic lesions of the bones, unless the two diseases be coincident. The boggy character of the swellings, the occurrence of superficial hemorrhages, and the stomatitis when the teeth are present are symptoms which readily establish the diagnosis. The gastrointestinal symptoms are usually more pronounced in rickets than in scurvy.

Purpura in its various forms resembles the disease in question in the presence of petechial hemorrhages, but the deep-seated extravasations beneath the periosteum and the other manifestations of the disease are wanting.

Some cases have been mistaken for infantile palsy on account of the pseudoparalysis, but careful examination, together with the history of sudden onset and the absence of marked pain and tenderness after the disease has become developed in spinal palsy, makes the diagnosis easy.

Congenital syphilis is distinguished by the absence of the hemorrhages, the mouth symptoms, and the extreme tenderness, while the stigmata of the syphilitic taint are rarely absent.

Prognosis.

The prognosis is favorable in cases in which the disease has been recognized early and in which the proper treatment has been instituted. According to Barlow, the duration in cases placed on treatment is on the average from two to four months; but Rotch states that he has usually seen recovery in two or three weeks, even in severe cases, when energetic treatment has been resorted to.

Treatment.

Diet is of first importance. The prevention of the disease is secured by a proper regulation of the diet in all cases from infancy to the second year, and particularly by the proper regulation of the food so that its character may vary from time to time with the altered requirements, with the age of the child, and the like. The sterilization of milk does not seem to have the importance in causing this disease attributed to it by some, though the overheating of milk is never desirable. After the disease has been recognized, the food should be regulated according to the age of the patient and the condition of its digestion. Certain special articles of diet, however, must never be neglected in this condition, as they have been found almost specific in their action. Among these may be ranked the

juice of oranges, grape-juice, finely scraped apple pulp, and fresh-meat juice. From two to four tablespoonfuls of the juice of the orange or of grapes may be given in the twenty-four hours and corresponding quantities of the other articles named. Excellent results have been obtained by the daily administration of a purée made of potato and milk, and doubtless a more general use of such a preparation in children beyond the first year of life would prevent many of the cases of this disease.

Drugs possess practically no value as remedies having direct control of the disease, but tonics may be useful in building up the condition of the blood or of the system after the progress of the affection has been arrested. Iron in the form of the iodide, or tonics, such as calisaya and gentian, may be used, and minute doses of arsenic are desirable.

Hæmophilia.

Synonyms.—Hæmatophilia; morbus hæmaticus; diathèsis hæmorrhagica; bleeders' disease. The term "bleeder" is applied to the patient.

Definition.

Hæmophilia is characterized by a tendency to spontaneous hemorrhage or bleeding on trivial injury, the disease being practically always hereditary in nature. The hemorrhages are generally severe and often uncontrollable; and the patient usually suffers with rheumatoid swellings and pains in the joints. The disease, as a rule, lasts throughout life, generally becoming less marked with advancing years.

History.

Hæmophilia was probably known to the ancient writers, in evidence of which a passage in Lucan has been cited by Legg. A more positive reference to the disease is found in a passage in the writings of Alzaharvi, a physician who died in Cordova, 1107 A.D. Another reference is made to it by Benedictus in 1539, and, according to Virchow, Hochstetter described a case in 1674. The first reliable description of a bleeder family is that of Fordyce published in 1784, while Rave contributed to the history of the affection records of bleeders published in 1798. Otto, in 1803, gave an account of cases occurring in a family through several generations in New England, and referred to instances observed by Rush in Maryland, while other American physicians undoubtedly recognized the disease at even earlier dates. The celebrated Appleton-Swayne family, of Reading, Mass.,

was first recorded by Hay, in 1813. Among the more important contributions to the subject of a systematic character are those of Nasse, Schönlein, Wachsmuth, Grandidier, Legg, Simon, and Dunn.

Etiology.

Heredity.—The most important fact in the etiology of this affection is its hereditary characteristic, and at the present time practically all cases admitted to be instances of hæmophilia give evidence of this etiological factor. Undoubtedly it would seem reasonable, as Eichhorst suggests, that the disease may arise *de novo* at the present day as well as formerly; but as yet no instances have been recorded of cases in which the disease has occurred in a person whose family had presented no signs of the affection, while in the progeny of the patient himself the disease has been propagated. The frequency of cases in individual families varies very greatly. The average, however, may be estimated from the fact that the collected statistics of Grandidier show six hundred and fifty-seven cases in two hundred families. In some of the celebrated families of bleeders, however, in which the disease has been known to exist for a number of generations, the average seen in Grandidier's statistics is greatly exceeded; but the exact figures are difficult to obtain, for obvious reasons.

Legg in his monograph tabulates the transmission in the celebrated Clitherow family, in which hæmophilia had existed for two hundred years; in the families of Tenna, Switzerland, as many as five generations have been affected, while in the Appleton-Swayne family Brown states (in a letter to Osler) that cases have now occurred in the seventh generation.

The manner of transmission varies somewhat, though in most instances a peculiarity of transmission first noted by Otto is observed. The characteristic of this is the fact that while the female members of a family are unaffected by the disease they transmit it to their male offspring. This is almost the rule, although occasional exceptions have been observed. Thus, in the family reported by von Limbeck, in which the disease had existed during four generations, only the daughters were affected during the earlier period, while in the later generations the males alone presented the disease. Sometimes throughout the entire history of a family the transmission may be direct from father to son, grandson, etc.; at other times from father to daughter, granddaughter, etc.; and finally one or more generations may entirely escape, and the disease presents itself in subsequent offspring.

Regarding the occurrence of hæmophilia in persons giving no

family history of the disease, it is interesting to note that certain instances have been recorded by Foerster and others in which the marriage of blood relations has seemed to lead to the development of hæmophilia in the offspring. Similarly it has been held by certain writers that maternal impressions are of importance, and occasionally certain constitutional diseases in the parents appear to be significant. Among these gout, rheumatism, scrofula, and tuberculosis have been noted by systematic writers, but, as has been already observed, the nature of the cases occurring in such conditions has not as yet been sufficiently determined, and the subsequent transmission of the tendency by such persons has never been observed.

Sex.—In the statistics published by Grandidier, of 657 cases 609 were males and 48 females, or a proportion of 12.7 : 1. As has already been observed, such a proportion is not always observed, though it is the rule. Doubtless in some instances, as Koch contends, hæmophilia in females is designated by other names, such as profuse menstruation, purpura, etc., but after making all allowances the overwhelming majority in the male sex is established.

Age.—In the great majority of cases the disease begins in early life. Thus, in the statistics of Grandidier, among 113 cases 63 began in the first year, 17 in the second, and 13 in the third year. It is unusual for the manifestations to present themselves after the first decade of life, but instances have been recorded in which the patient has passed his twentieth year before the onset. Thus, in the cases of Simon, both father and son had reached the age of twenty-two years when the disease began.

The present seems a favorable opportunity for alluding to certain hemorrhagic conditions of the newborn. These have been variously termed *transitory hæmophilia*, *spontaneous hemorrhages of the newborn*, *infectious hæmophilia of the newborn*, and *hemorrhagic disease of the newborn*. The manifestations in these cases usually occur in the early weeks of life, run an acute course, and terminate either in death or in complete recovery. Cases of this character have been studied by Klebs, Ritter, Eppinger, and Townsend. The latter collected fifty cases, in all of which excepting three the hemorrhage occurred within the first seven days of life, and in these three on the eighth, ninth, and fourteenth days respectively. The duration in the cases which recovered was never above nine days, and two-thirds of all recovered within five days. In the fatal cases the children died within twenty-four hours in half of the cases, and within the first week in all of the rest but one, which died on the eighth day. The mortality was sixty-two per cent. The hemorrhages occurred from the gastrointestinal tract alone in 19 cases, from the umbilicus alone in 3, and in the

skin alone in 6. In 20 cases there were hemorrhages from the intestines, in 14 from the stomach, in 14 from the mouth, in 12 from the nose, in 18 from the umbilicus, and in 21 from the skin. The temperature in cases in which it was observed was nearly always elevated.

The transitory character, the occurrence of spontaneous hemorrhages in different parts of the body, the acute course, the self-limited character, and the frequency of umbilical hemorrhages, together with the early appearance of the disease, make it extremely likely that the affection under consideration is not to be classed with true hæmophilia, but rather as a separate group of conditions, probably for the most part infectious in character. It bears close relations with purpura hæmorrhagica, though in most instances purpura is not a striking symptom.

Frequency and Geographical Distribution.—The number of cases reported in the statistics alluded to illustrates the frequency of this disease. It occurs in all parts of the world and does not vary greatly in frequency in different situations, though perhaps it occurs more commonly in northern countries and on exposed sea-coasts than elsewhere. It would appear to be somewhat more common among the Anglo-Germanic nations, according to the statistics of Grandidier, but this predisposition is not marked. The influence of climate appears to be potent also in determining the individual attacks, and the season of the year exercises a like influence. The attacks are particularly prone to occur during the spring and fall, when the weather is changeable, and in situations in which the climate is cold and damp, and in individual cases the susceptibility to meteorological conditions may be quite striking.

Infection.—Certain observers have claimed that hæmophilia is an infectious condition, but the evidence in favor of such a view is extremely scanty. It is conceivable, of course, that certain individuals are more prone to hemorrhagic manifestations in consequence of various forms of infection, and that the manifestations of hæmophilia may occur at such times, but the constant and apparently unvarying liability to hemorrhage observable in this disease cannot well be reconciled with our views of infection, and in addition to this it may be noted that bacteriological studies have proved entirely negative.

Pathological Anatomy.—Practically no lesions are observed in this condition, excepting the hemorrhages or results of hemorrhage. As most of the cases die of loss of blood, the organs at the post-mortem examinations usually present an anæmic appearance. The heart is empty of blood clots or almost completely empty. In some instances the foramen ovale has remained patulous or the ven-

tricular septum has been incomplete. No connection, however, can be established between these conditions and the disease in question, unless these occurrences be taken as indications, with the hypoplasia of the aorta first observed by Virchow, of a general vascular insufficiency. The wall of the aorta has sometimes been found extremely thin and the lumen of the artery unusually narrow. In addition to this, spots of fatty degeneration have been found in the intima. Occasionally the other arteries are visibly deficient in calibre or in the thickness of their walls, and this may occur as a uniform process or in localized areas. A number of authors have found changes in the capillaries which may possibly be in some way related to the alterations in the larger vessels just noted. Thus v. Buhl called attention to the unusual richness in capillaries of the skin and subdermal tissues, though in the instance reported a distinct disease of the skin was present. Birch-Hirschfeld found enlargement or swelling of the endothelial cells of the capillaries, the nuclei of the cells being considerably increased in size and the protoplasm containing granular areas. In general, the spaces between the endothelial cells seemed unusually capacious. Kidd found a proliferation in the endothelium of the capillaries and swelling of the fibres and nuclear multiplication in the media. These examinations, however, have been too few and too lacking in uniformity to warrant the changes being accepted as characteristic lesions of the disease.

The solid organs show no evidences of disease excepting the heart, which has been found fatty by several observers. Hemorrhages, however, may occur in the various situations.

The blood presents no characteristic features. Grandidier, Lossen, and others claimed that the coagulability is decidedly decreased, but others have asserted that this view is unfounded. Undoubtedly, as numerous observations indicate, the blood does coagulate in cases in which slow hemorrhage occurs and may form clots of considerable size. The objection has been made to the view of Grandidier that his observations were made at a stage when considerable loss of blood had been sustained. This, however, as Grawitz points out, would furnish confirmation rather than disproof of his view, since the normal blood tends to increase in coagulability when hemorrhage takes place. Recent studies of Alexander Schmidt and v. Manteuffel would indicate that there is actually decreased coagulability, since the blood required four and one half minutes to form a clot; whereas the addition of Schmidt's zymoplastic substance led to rapid coagulation in ten seconds. This corresponds also with recent studies of A. E. Wright.

After the hemorrhages the blood becomes thin or hydræmic, and may be visibly light colored. The usual changes brought about by

hemorrhage, reduction in the red corpuscles, reduction in the hæmoglobin, and increase in the number of leucocytes, may be observed and vary in degree according to the amount of hemorrhage.

In a recent study Albertoni claims to have found that the red corpuscles are prone to break up more readily than normal erythrocytes and that the blood-vessel walls are excessively friable.

Immermann expressed the belief that hæmophilia is in reality a condition of plethora, the quantity of blood being excessive and the hemorrhages being evidences of the tendency of the blood to make its escape. Other observers have found increased numbers of red corpuscles, but neither of these views can be accepted.

It is, however, to be noted that the loss of blood in hæmophilia seems to be more readily borne than by persons in perfect health.

Pathogenesis.

The nature of hæmophilia remains entirely obscure. It is possible that the hemorrhages may be the result of changes in the blood or in the blood-vessel walls, the evidence, so far as such has been obtained, pointing to an increased permeability and friability of the smaller vessles and a lessened ability of the blood to form firm clots. The changes which have been discovered in the blood-vessel walls have already been referred to. They are far too varying in character to make it seem likely that these constitute the essential lesions. It is more likely that the changes are of a chemical sort, as Eichhorst has maintained, and that they are undiscoverable by our present methods. That the conditions are local or in the vessel walls rather than in the blood itself would seem to be evidenced by the remarkable case of Senator, in which the hemorrhage in a case of renal hæmophilia occurred from one kidney alone, and in which the disease was definitely arrested by the removal of the affected kidney. A similar deduction may possibly be drawn from the remarkable case related to Osler by D. Hayes Agnew, in which bleeding occurred only from cuts above the neck and never from those below this part.

Symptoms.

The onset of the disease occurs, as has already been stated, in childhood. The first evidence may be a severe and fatal hemorrhage. This may occur during or immediately after the birth of the child, as occurred in one case under my observation, the hemorrhage in this instance coming from an abrasion produced in the infant's mouth in the delivery of the after-coming head. The cutting and

tying of the umbilical cord and the separation of this rarely give rise to excessive bleeding.

The hemorrhages of hæmophilia may be traumatic or spontaneous.

The *traumatic hemorrhages* are frequently caused by injuries so trivial that under ordinary circumstances they would be overlooked entirely. In numerous instances a scratch or the prick of a pin, or slight abrasions of the surface occurring in young infants, have furnished the first evidence of the disease, and, as Fordyce remarked, larger wounds sometimes prove less dangerous than slight injuries. Indeed, it has been found in some cases that enlargement of a small wound by free incision has served to check the hemorrhage. Slight surgical operations, such as snipping the frænum of the tongue or circumcision, frequently lead to the first hemorrhage. In other cases, and very commonly, the disease begins during the first dentition, the hemorrhages occurring with the eruption of the teeth.

The blood usually escapes in a steady stream flowing from the substance of the tissues as a parenchymatous hemorrhage rather than from the larger vessels. The arteries are very rarely the source of the bleeding. The loss of blood sometimes proves enormous and the patient may rapidly become exsanguinated. Finally syncope may occur from the loss of blood and the hemorrhage may then cease. In other cases cessation does not take place and death occurs from anæmia of the brain.

When the injuries upon the surface are very slight and the cellular tissues loose, the blood may collect beneath the surface, forming large masses or blood tumors, in which the blood remains in a fluid condition for a considerable length of time.

Spontaneous Hemorrhages.—The most frequent source of spontaneous hemorrhage is the nose, epistaxis being recorded in one hundred and sixty-nine of three hundred and thirty-four cases in which the source of the hemorrhage was noted in Grandidier's statistics. In many of these instances doubtless there was some unsuspected traumatism, but in the majority of cases of epistaxis the hemorrhage is spontaneous. Hemorrhages from the other mucous surfaces are less frequent. In women the disease may manifest itself in the form of profuse menstruation, and sometimes the establishment of the menstrual function occurs much earlier than is customary; or again there may be free hemorrhages from the vagina in girls before the establishment of menstruation. Furious hemorrhages may occur during labor, but on the other hand cases are not rare in which this process is unattended by great loss of blood, and the apparent freedom of the female sex from the disease renders labor of comparatively little consequence. Hæmatemesis and hemorrhages from the

bowels are quite common, and may be attended by or preceded by mild gastrointestinal disturbances. Hæmaturia occurs in a small proportion of cases, and a few remarkable instances of so-called *renal hæmophilia* (Senator) have been recorded in which the bleeding occurred from one or both kidneys and in which the examination of these organs showed no pathological change. In Senator's case the hemorrhage was found to come from but one kidney and ceased after removal of the affected organ.

Hemorrhages into the skin may be the result of slight traumatisms which have been overlooked, such as those due to the pressure of clothing; but they may be entirely spontaneous. In most instances small petechial extravasations are formed, but large suggillations or considerable collections of blood in the subcutaneous tissues may be observed. In the latter instances the blood tends to remain fluid, and not rarely, surgical interference being undertaken, fatal hemorrhages have resulted. Sometimes abscess formation occurs. The ecchymoses are most frequent on the extremities, but may affect the trunk as well; the face usually escapes. Hemorrhages into the serous surfaces are not unusual. Large collections of blood may be found in the peritoneal cavity, the pleura, or the pericardium. Hemorrhages into the brain or between the meninges usually occasion serious manifestations, such as attacks of unconsciousness, epileptiform convulsions, and palsies.

The joints frequently become swollen and painful, and in these cases muscular cramps or pains may coexist. The conditions of the joints may depend upon small hemorrhages into the capsule or into the synovial membranes, and the painful condition surrounding the joints and in the muscles may be the result of extravasations in these situations and possibly also in the nerve trunks. Inflammatory changes in the synovia are not unusual in cases in which considerable hemorrhage has taken place. The joint in such instances may become greatly swollen, giving the appearance of some forms of tuberculous arthritis, but the skin over the affected part is usually discolored by extravasated blood. In the later stages ankylosis and deformities may result. The joints most frequently involved are the knee and the elbow.

The general appearance of the patient suffering with hæmophilia may be in nowise distinctive, although the older writers gave detailed descriptions of the *habitus hæmophilicus*. Among the characteristics noted were a pale complexion with thin skin, light blond hair, bright eyes, and in general a delicate organization. Variations, however, from this description are exceedingly common. After the occurrence of hemorrhages the patient becomes extremely anæmic and frequently

suffers with severe palpitations, dyspnœa, vertigo, attacks of faintness, and other evidences of the bloodless condition.

On physical examination enlargement of the heart may be detected and systolic murmurs may be heard at the cardiac base and in the vessels of the neck. The urine frequently contains albumin after the hemorrhages, and according to some observers it is rich in phosphates and poor in urea. These claims, however, have not been substantiated and are of no practical significance. Sometimes the urine contains large quantities of blood, and in certain cases, as in those of Senator and others already alluded to, hæmaturia may be the only expression of the hemorrhagic diathesis. The occurrence of fever in hæmophilia has been frequently observed, but is by no means uniform. Attacks are most apt to occur in cases in which large hemorrhages have taken place into the tissues, and particularly when the joints have been affected. Secondary inflammatory changes in the joints or serous surfaces, or abscess formation may lead to the development of a continuous or irregular fever.

Course and Prognosis.

After the first hemorrhages have occurred, the disease or the tendency to hemorrhage continues throughout life. In cases in which the hemorrhages are never severe and in which middle life has been reached the tendency may practically disappear in the later years, and many instances are recorded in which hæmophilic individuals have lived to extreme old age. Among other cases Simon refers to three persons who had reached the ages of seventy, eighty, and ninety-four years respectively. Climate and the condition of the general health may cause some variation in the liability to hemorrhage and in the severity of the hemorrhages when they occur, but such influences are not easily estimated. The prognosis is worse in the male sex than in the female sex. Of one hundred and eighty-one cases included in Grandidier's statistics one hundred and fifty-two terminated before the close of the seventh year. According to Legg, the disease is rarely fatal in the first year.

Diagnosis.

Difficulty in diagnosis arises in cases in which the disease occurs in quite young children or in women. The history of the case is always of prime importance, and when there is evidence of the disease in other members of the family any unusual tendency to hemorrhage will naturally be regarded as due to hæmophilia.

Particular interest attaches to the forms of hemorrhage occurring in the newborn which have been already alluded to. These distinguish themselves from true hæmophilia by their transitory character, by their self-limited course, by the frequency with which the bleeding occurs from the umbilicus, and by the frequent association of jaundice and high fever. All of these characters give the condition in question the manifest appearance of an infectious disease and serve to distinguish it from true hæmophilia.

Purpura in its rheumatic or hemorrhagic forms and scurvy are usually easy to distinguish by the absence of suggestive history and the occurrence of these conditions in persons debilitated by previous disease or by improper diet or surroundings.

The joint manifestations of hæmophilia may resemble tuberculous arthritis very closely. The diagnosis can usually be made from the associated symptoms, the hemorrhagic discolorization of the skin near the affected joint, and from the history.

Treatment.

Prophylaxis may be of some value, though it is difficult to guard against injuries which may lead to hemorrhages in affected individuals. When it is known that the individual is liable to become a bleeder every safeguard should be established to prevent injuries, and slight surgical operations, such as lancing the gums, circumcision, the extraction of teeth, vaccination, and the like, must be avoided or undertaken only in case of urgent necessity. Regarding vaccination, it may be pointed out that this, as a rule, has not given rise to hemorrhages, though cases have been reported in which fatal hemorrhage occurred from this cause (Strohmayer, Henoch). The extinction of the disease by regulation of the marriage of bleeders is unfortunately impracticable. Wherever it is possible to prevent marriage, particularly of the female members of a family, this should be done, and in cases in which the disease is pronounced in type it should be insisted upon.

After the occurrence of injuries and before the hemorrhage has become severe, the patient should be put at absolute rest and the wound should be dressed. In many cases this may suffice to allay the hemorrhage. Unfortunately, however, this is frequently not the case. Among other measures which may then be instituted the application of ice and of various hæmostatic remedies is to be mentioned. The more powerful styptics have the disadvantage in small hemorrhages of causing small clots, which in their subsequent separation lead to more serious hemorrhage than that which occurred before. Never-

theless, the solutions of the perchloride of iron have been frequently employed and have sometimes been beneficial. Even the cautery may be resorted to and may cause arrest of the hemorrhage, but the danger of secondary hemorrhage is more pronounced in this case than when styptics are used. Rest, cold, and compression are upon the whole the more useful methods of treatment. In the case of epistaxis plugging of the nostrils may become necessary after solutions of tannic acid or gallic acid and the application of ice water have been tried.

Recently certain physiological principles regarding coagulation have been applied to the treatment of the hemorrhages in this disease. A. E. Wright has recommended the local use of a solution of fibrin ferment in an aqueous calcium-chloride solution. Von Manteuffel and Schmidt have reported an instance in which hemorrhage from the gum after extraction of a tooth was controlled by the application of a solution of cocaine followed by Schmidt's zymoplastic substance. The preliminary use of cocaine is necessary to cause temporary contraction of the blood-vessels and partial control of the hemorrhage, so that the zymoplastic substance may be given an opportunity to operate. The same authors object to the injections of fibrin ferment solutions in calcium chloride, recommended by Wright, on the ground that this would expose the patient to the danger of ferment intoxication.

A great variety of remedies have been used internally in the belief that they have exercised a controlling influence upon the hemorrhages or upon the tendency to hemorrhages. Among such remedies ergot, acetate of lead, perchloride of iron, and mineral acids, particularly aromatic sulphuric acid, may be named. There is little evidence, however, that any of these exercises a potent effect. More may be expected of the continuous use of calcium in the form of calcium chloride, lime water, or other salts. In several instances reported this has served to control the tendency so long as the patient has continued using the remedy; while in experimental investigations it has been found by Wright that the coagulability of the blood of persons liable to hemorrhage has been considerably increased by the internal administration of calcium chloride. Magnesium sulphate and sodium sulphate in purgative doses appears to exercise a favorable influence in some cases, both in the way of preventing hemorrhages and also in controlling them after their onset. The action in this case is probably one of inspissation of the blood.

During the continuance of the hemorrhage the patient must, of course, be kept absolutely at rest and in a horizontal position; and at times it is necessary to elevate the feet so as to obviate the danger

of anæmia of the brain. In such cases saline transfusions may be necessary to prevent extreme depletion of the circulation, and in a case recorded by Pearl life was saved by this procedure. It must be remembered, however, that the introduction of the needle into the skin for the purpose of saline injection may be the occasion of further hemorrhage into the subcutaneous tissues, or from the puncture, and thus increase the original trouble. This applies even to the introduction of a hypodermic needle, as in one instance in which hemorrhage from the gums occurred I have seen enormous subcutaneous hemorrhage filling the loose areolar tissue of the arm almost completely after the introduction of a hypodermic needle for the purpose of administering ergotin. It may, therefore, be advisable to practice enteroclysis before hypodermic injection of saline solutions is resorted to.

After the cessation of the hemorrhage the patient should be placed under the most favorable conditions and, when it is possible, a residence in a warm climate should be recommended. Tonics such as cod-liver oil, arsenic, and iron may be useful to improve the condition of the blood.

RACHITIS.

BY

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RACHITIS.

Synonyms.—Rickets, morbus anglicus, articuli duplicati, *rachitisme, nouures.*

Definition.—Rachitis (also spelled rhachitis) is a general disease, *totius substantiæ*, characterized by deformities of the skeleton (bending of the diaphyses, swelling of the epiphyses, the "rachitic rosary" or enlargements at the junction of the ribs with their cartilages) which give to it a peculiar physiognomy enabling one to recognize it on sight.

History.

During the first half of the seventeenth century a disease, hitherto unknown, invaded the whole of England, after having first raged for a time in the counties of Dorset and Somerset. The attention of the Royal College of Physicians was called to the disease, and it appointed a commission of eight members to investigate and report upon it. This report, prepared by Glisson, Bate, and Regemorter, was published in 1650, under the title: "De Rachitide, Tractatus Opera Primo ac Potissimum Glissonii Conscriptus, Adscitis in Operis Societatem Bate et Regemorter," Londini, 1650. This is the earliest known publication on the subject of rickets, and the history of the disease does not go back beyond this time; but when we consider the dyscrasic origin of the affection, which is a true *maladie de misère*, we are forced to refer its origin to a more remote period. Nevertheless, Glisson was the first to describe the disease, and his name should ever be preserved in connection therewith.

On the Continent of Europe the term morbus anglicus or morbus Anglorum (or the equivalent in the modern tongues) has long been synonymous with rachitis. In England and America the popular name of the disease is rickets, derived from the Norman term *riquets*, applied to persons suffering from kyphosis or other deformities. The Greek term, rachitis, proposed by Glisson and adopted in France (*rachitisme*), is a less happy one, for it suggests a rather rare localization of the disease in the spine, vertebral gibbosity. It is very possible, however, that in Glisson's time Pott's disease of the spine was not always differentiated from rachitis, for the diagnosis sometimes

presents considerable difficulty. The word *chartres* (carcer, castrum) was formerly quite extensively employed in France, suggesting the idea of an interference with, or deprivation of, liberty caused by the disease. At the present day the common people in France speak of *nouures* (knottings) and of *enfants noués*, being struck especially by the epiphyseal swelling. The same symptom has found expression in names applied to the affection in all languages—double joints, *doubles jointures*, *doppelte Glieder*, *articuli duplicati*, etc.

After Glisson, who had well described the symptoms of the new disease, Mayow, of Oxford (1660), called attention to an important characteristic, namely, the softening of the bones. Later J. L. Petit (1741) emphasized the evil consequences of premature weaning. Duverney ("Maladies des Os," 1751) described the pathological anatomy of the disease, and showed that the bones in rachitis are softened, rarefied, lighter than normal, more tender, more fragile, more liable to suffer a green-stick fracture. He showed that the bones were rough and uneven on their surface, that they were covered in places by a new layer, that they were riddled with holes, etc. Portal (1797), led by certain morbid coincidences, divided the disease—which had hitherto been regarded as a morbid entity—into seven varieties, viz.: syphilitic, scrofulous, scorbutic, rheumatic, following intestinal lesions, and following the exanthemata. He used mercury in the treatment of the affection.

The physicians of the nineteenth century have described with greater definiteness than their predecessors the symptoms, course, etiology, pathogeny, etc. Rufz (*Gazette Médicale de Paris*, 1834) showed that there is a reddish, elastic, reticular tissue in rachitic bones which Jules Guérin (1837–39) called spongoid tissue. This last-named writer describes three stages of the disease, as follows: (1) Period of incubation or of effusion, in which the blood becomes distributed throughout the interstices of the osseous tissue; (2) period of deformity in which the spongoid tissue invades the epiphyses, diaphyses, and the subperiosteal space, and the bones soften and bend; (3) period of resorption, of consolidation, and of eburnation, in which the spongoid tissue becomes compact and the bone very hard. To these three periods he added later a fourth, not constantly present, in which the osseous tissue remains fragile and rarefied—the period of consumption. He attempted to make animals rachitic by changing their alimentation, and claimed to have succeeded in so doing in the case of puppies. His anatomical studies and his experiments mark an epoch in the history of rachitis.

Trousseau and Lasègue (*Archives de Médecine*, 1849) and Beylard (Thèse de Paris, 1852) published remarkable works on rickets in

which they indicated its points of resemblance to osteomalacia. Broca (Société anatomique de Paris, 1852) showed that rachitis, as regards the bones, is only a deviation, an arrest, a suspension of normal osteogenesis, and he was the first to describe the histological lesions of the disease.

Virchow (1853), taking up the study of the rachitic process, pointed out its analogies to parenchymatous osteitis. Kassowitz and Baginsky appear also to have adopted this view of the nature of the affection.

Parrot (International Medical Congress of London, 1881), throwing aside all the preconceived notions of the disease, claimed to prove anatomically and clinically that rachitis is always a consequence of syphilis. This opinion, although ably presented, has not obtained general acceptance. I have endeavored in a previous work ("Le Rachitisme," Paris, 1892) to show in what respect this theory was wrong.

The view that rickets is dependent upon a previously existing affection of the digestive tube, gastro-intestinal dyspepsia, or gastric ectasia, so frequently present in sufferers from the disease—a view which I believe to be the correct one—will be presented in detail in the section on Pathogenesis.

Pathological Anatomy and Physiology.

In rickets everything is diseased, all the tissues and all the fluids of the body have undergone a change in their structure or in their biochemical action. These lesions are, however, specially marked on the side of the bony framework, and it is therefore in a consideration of the changes in the bones that we will begin our study.

For many authors rachitis is simply a disease of the locomotor apparatus, falling therefore in the domain of the surgeon or orthopedist. But it is so only in appearance, for the bones are not the first or the only organs attacked, and physicians have always disputed with surgeons the propriety of their management of the disease, which consequently enjoys the distinction of being treated in all treatises, whether they be strictly medical or purely surgical in character.

The lesions of the bones are visible to the naked eye in well-marked cases, but always are to be seen on microscopic examination. The long bones are curved or rotated on their axes, sometimes sharply bent at several points; the epiphyses at the wrists and ankles are swollen; the vertebral column may be deviated posteriorly (kyphosis) or laterally (scoliosis); there are swellings on each side

of the sternum at the junction of the ribs with their cartilages (rachitic rosary); the ribs are sunken in laterally, thus narrowing the thoracic cage and throwing the sternum forward (chicken breast); the flat bones of the skull and of the pelvis are also deformed, bent inwards, etc.

All these bones when removed from the soft parts appear rarefied, spongy, lighter, softer, and more friable than in the normal state. Trousseau has insisted upon the lightness of the bones. Even after the morbid process is concluded and rarefaction has given place to eburnation it will be found that the rachitic femur, for instance, weighs less than a normal femur of the same size. The entire skeleton of a rachitic child of eight years examined by Trousseau weighed only one kilogramme instead of seven or eight, which is the ordinary weight.

In extreme cases the bones are soft and flexible, and may be bent like green wood. Their surface preserves the impression of the nail; their tissue can be cut with a knife. This diminished consistence of the bony framework explains the spontaneous fractures, which are rather frequent in severe forms of rachitis.

Stages.

Following the example of Jules Guérin we may describe three stages in the anatomical evolution of the disease:

1. *Effusion and Rarefaction.*—The bones not yet deformed are more elastic and less hard than in health; the periosteum is thick, vascular, adherent to the roughened and irregular surface of the subjacent bone. If we cut this bone we see that its areolæ are dilated, filled by a blood-stained matter resembling gooseberry jam. This jelly-like material is found also in the medullary canal, under the periosteum, and between the separated layers of the diaphysis. This is what is called the medullization of the bones. The cartilage which separates the diaphysis from the epiphysis is itself thick, bluish, softened, and may be detached by the action of water.

The same areolar condition and the same medullization are found in the flat bones: the bony tables are thinned while the diploë is swollen and succulent. The same condition is present also in the short bones. All the bones when dried are seen to be porous, friable, rarefied, and decalcified.

2. *Deformation and Organization of the Effused Material.*—If the changes above described continue to increase, the bones yield to muscular action and to pressure, becoming deformed, curved, flattened, twisted, and may be cut into strips. Water injected into the bone will traverse the lamellæ and fill all the areolar cavities. It is in this

stage that the epiphyses become swollen, that the rachitic rosary is formed, and that the diaphyses become curved. In the concavity of these curves the periosteum is thicker, more vascular, and more firmly adherent than on the convex side; a new osseous formation separates it from the old bone. The medullary canal has neither the same calibre nor the same extent, nor the same direction; it may be obliterated or it may open externally at the apex of the convexity, when the curve is very pronounced, and we may thus see the two ends of the medullary canal join at an obtuse angle at the apex of the curvature. Usually it is narrowed in its central portion and dilated at the extremities, having somewhat the form of an hour-glass.

It is during this stage also that the spongoid tissue of Jules Guérin appears—the swollen bones suggest a sponge, a biscuit, or gluten bread. We find a reddish reticular layer resembling a fine sponge between the epiphyseal cartilage and the spongy diaphyseal tissue. The fractures, complete or incomplete, spontaneous or resulting from slight traumatisms, sometimes intra-uterine, are due to these lesions. These fractures, ordinarily subperiosteal, unite readily sometimes with an excess of callus; but they may terminate in a pseudarthrosis. The long bones are exposed to fracture; the flat bones, especially those of the vault of the cranium, present spots of softening and of spontaneous perforation—the craniotabes of Elsässer (1843). This craniotabes or craniomalacia affects the occipital and parietal bones, and the petrous portion of the temporal bone, but very rarely the frontal. The lime salts are absorbed, leaving the dura mater and the periosteum almost in contact; the bone is replaced by a soft and depressible fibrous layer which leaves the brain without protection against external injury.

3. *Consolidation and Eburnation.*—After this longer or shorter period of disorganization and destruction comes the stage of reparation, but the first is not necessarily concluded before the second begins. The new tissue effused beneath the periosteum, between the layers of the diaphysis, in the epiphyseal areolæ, becomes organized and calcified. The bones then become harder at the same time that they become straighter, and the nodosities gradually become less marked. The bone often becomes harder and denser than normal—eburnated. The osteoid tissue described by Virchow is replaced by osseous tissue.

4. *Consumption.*—In some cases this reparation does not take place, the bones remain spongy and rarefied and their areolæ become filled with fat; they are then excessively porous, light, and fragile.

Microscopical Examination.—Broca was the first to give us a satisfactory histological description of the osseous lesions of rickets. He

takes for comparison the process of normal ossification. The dia-epiphyseal cartilage, which is the active agent in the growth of long bones, passes, before arriving at the condition of perfect bone, through the intermediate stages called chondroid and spongoid. This layer of pearly hyaline cartilage, which separates the body of the bone from its head, becomes more opaque and thicker, proliferates, and becomes transformed into spongy tissue with fine, brittle trabeculæ before becoming compact tissue. In rachitis the ossification is interfered with; the chondroid and spongoid tissues accumulate at the extremities of the diaphysis without undergoing their final osseous transformation. In the case of the short and the flat bones no spongoid tissue is formed, but medullization occurs with softening and decalcification. Let us imagine a vertical section of the extremity of a long bone in process of growth—of the femur, for example. Between the diaphysis and the intermediary cartilage is seen a bluish layer one-half to two millimetres in thickness; this is the normal chondroid layer. It is formed of primary cartilaginous capsules containing secondary capsules in parallel rows separated from each other by "rivers" of a granular substance. This is the "rivulation" of Broca. The lime salts are deposited first in the midst of these tracts or "rivers" of granular substance, and then in the primary capsules. The secondary capsules are dissolved, the cells which they contain proliferate and fill the primary capsules, which finally form communications with each other through partial absorption of the calcified partitions which separated them. This is the normal spongoid layer which has succeeded the chondroid layer. Then the vessels penetrate this layer, canaliculi are formed, and the manufacture of bone is thus accomplished.

We shall see now how rachitis disturbs this process of normal ossification. The normal chondroid layer or layer of proliferated cartilage increases greatly, attaining a thickness of from four to twelve millimetres instead of one or two. The normal spongoid layer or layer of proliferated and calcified cartilage is also thicker; it is, as it were, mortised with the preceding, and there may even be separate islets of the spongoid tissue in the substance of the chondroid substance and vice versa. The vessels are dilated. Beneath this layer appears a red, vascular, spongy tissue having the appearance of bone partially softened by acids. The secondary capsules of the proliferated cartilage are not dissolved but become calcified; the vessels increase in size, anastomose with each other, and form a cavernous tissue. Under the periosteum the exuded material is transformed into connective tissue and then into osteoid tissue (Virchow). When the diaphysis becomes curved the osteoid tissue accumulates in

a thick layer in the concavity of the curve but remains thin on its convexity. This tissue is also deposited under the periosteum of the flat bones. In the short bones we find a no less marked disturbance of ossification: islets of cartilaginous tissue surrounded by the spongoid substance are seen here and there, the vessels are more numerous, and the rarefaction of the bone is very evident.

To recapitulate: the intermediary cartilage which is concerned in the growth of the long bones passes, before becoming perfect bone, through two transitory stages—chondroid and spongoid. The chondroid tissue is proliferated cartilage; the spongoid tissue is proliferated and ossified cartilage. These transitory stages become permanent in rachitis.

A. Pollosson has noted in cases of cured rachitis the persistence of little cartilaginous pearls in the midst of the epiphyseal osseous tissue; and this was also noted by Broca. The long persistence of these cartilaginous granules might explain the late deformities, such as genu valgum, coxa vara, the exostoses, and the scoliosis of adolescents. We should add that in what seems to be partial rachitis limited clinically to a single limb or a single bone, the lesions are generalized throughout the skeleton. Poncet, of Lyons, has insisted especially and justly upon this point: rachitis affects all the bones at once, but in unequal degree; it is the epiphyses, the growth of which is most active, which present the lesions in most marked degree.

Chemical Changes.

Chemical analysis of rachitic bones has shown a true inversion in the proportions of organic and inorganic constituents. Normally, the calcareous matter in bone represents two-thirds of the substance, the organic matter one-third only; but in rachitis the proportion is reversed, the mineral salts constituting not more than one-third of the entire mass. According to Baginsky the quantity of lime is decreased threefold or even more. This decalcification is the principal fact brought into relief by chemical analysis. The same condition exists in even greater intensity in osteomalacia, but here it is complicated with the presence of an excessive amount of fat. In addition to this decalcification Friedleben has found in rachitic bones a notable increase in the amount of water with a slight excess of fat and of carbonic acid. We must inquire what is the significance of this lime deposit noted in the rachitic skeleton, but first we must form certain deductions from the results of anatomical examination just mentioned.

The exaggerated vascularization, the medullization, the swelling, and the softening of the bones reveal a profound nutritive dis-

turbance which certain authors (Pommer, Tedeschi) attribute to the influence of the nervous system, which others (Kassowitz, Baginsky) group among the irritative and congestive processes, and which others, finally, regard as of infectious nature. Mircoli has found post mortem in the bones of rachitic subjects various pyogenic microbes (streptococci and staphylococci.) Chaumier regards rachitis as a specific contagious disease. The pathological anatomy of the affection, however, does not warrant such a conclusion, but accords better with the doctrine of a dyscrasia.

Visceral Lesions.

The lesions in the bones are preceded or accompanied by more or less marked visceral lesions. Glisson remarked upon the increased size of the abdomen. This big belly, which is habitual, not to say constant, is not due to a narrowing of the thorax with consequent depression of the diaphragm, but rather to dilatation of the stomach and intestines, and in a measure also to hypertrophy of the liver and of the spleen. I have repeatedly called attention to this gastric ectasia, the clinical signs of which I have noted in a great number of rachitic children and the presence of which I, with others, have also been able to verify post mortem. Huguenin, in a little rachitic patient of ten months and a half, noted the lower border of the stomach 2 cm. below the umbilicus; at the same time the liver was fatty and the spleen hypertrophied. Baginsky found the stomach softened and dilated in a child two years of age. Nothing is more common than to find gastric ectasia at the post-mortem examination of rachitic children, and it is very certain that this is the usual condition.

Enlargement of the liver and of the spleen is not uncommon; it may be complicated with hyperglobulia and leucocytosis (Luzet), and with hypertrophy of the lymphatic glands.

On the part of the respiratory organs we find lesions of a congestive and inflammatory nature. The deformity of the thoracic wall interferes with the action of the lungs, provokes emphysema, induces and aggravates bronchitis, pulmonary congestion, bronchopneumonia, etc.

The heart is occasionally compressed and displaced, and milk spots are often found on the pericardium.

The brain is not well developed, the cerebrospinal fluid is abundant, the ventricles are sometimes dilated; and nervous troubles are quite frequently observed, such as, for example, glottic spasm, convulsions, muscular weakness, and pseudoparalysis. The muscles also may become atrophied from disuse, the progress towards recovery being thereby delayed and rendered more uncertain.

In brief, everything is diseased in rickets, and although the osseous lesions have hitherto been chiefly studied they are far from being the only lesions.

Fœtal or Congenital Rickets.

When rickets declares itself before birth it can hardly have an anatomical evolution of the kind described by Broca. We find, indeed, the appearances common to all ages—decalcification, deformity, and fracture of the bones—but is the process the same in the two cases? Many cases of congenital rachitis may be referred to achondroplasty or an anomaly of osteogenesis. Porak and Durante (Société de Médecine et de Chirurgie Pratiques, June 14th, 1894) found as the only lesion in the case of a new-born child, who would have been pronounced by everybody as rachitic (having a soft skull, twisted limbs, and fragile bones), a marked rarefaction of the bones and a dilated medullary canal containing marrow surrounded by a thin layer of bone. This process of excessive resorption has nothing in common with the rachitis process. It is therefore not certain, in spite of appearances, that congenital rickets is the same thing as rachitis of early childhood, as it is also not certain that late rickets, the rickets of adolescence, is identical with the two just named.

Symptoms.

Rachitis is a chronic disease; its onset is insidious, its progress slow and prolonged, its termination distant. Some authors describe prodromes, such as general weakness, muscular inertia, pallor, and sweating about the head. Later the child ceases to walk or to stand erect. If it has not yet walked, it is remarked that it does not do so by the time that it should; or that if it learns to walk, it does so slowly and with difficulty.

But that which ordinarily precedes rickets is the gastro-intestinal dyspepsia of nurslings: diarrhœa and constipation, eructations, vomiting, distention of the abdomen, erythema of the buttocks, urticarial eruptions, etc. The dyspepsia itself arises from faulty alimentation, to which rachitis is ordinarily attributed.

But the disease may occasionally appear without prodromes, following acute affections which have profoundly disturbed the nutrition of the young child, such as the exanthemata, bronchopneumonia, etc.

Once present, rachitis is readily recognized by symptoms which disturb the plasticity of the body and the harmony of its contours. The disease may be manifested in one member, one bone, or one part of the trunk alone, and is then called partial; at other times it at-

tacks in more or less marked degree the greater number of all of the bones, being then general. Jules Guérin has stated as a law that the rachitic deformities appear in order from below upwards and that a deformity of one part of the skeleton implies deformity of all the parts below. This is not correct, however, for the signs of rickets often appear in the head or thoracic wall before any evidence of the disease is manifested in the extremities. It is this order from above downwards that I shall follow in my description of the disease.

Head.—In most rachitic children the head appears to be enlarged, the frontal bosses are more prominent (Olympian forehead), the parietal bosses are also exaggerated, and the head takes on a square and brachycephalic shape; the encephalic mass appears to be more voluminous than normal, and there is sometimes even hydrocephalus. The anterior fontanelle is almost always widely patent, and its closure, which normally occurs at the age of fifteen or sixteen months, will be retarded up to the second, third, or fourth year. Sometimes there is a projection at the site of the fontanelle, pulsating strongly, and a systolic murmur may be heard on auscultation; this is the cephalic souffle of H. Roger. The bones of the cranium are occasionally found softened throughout a variable extent as a result of a precocious decalcification which may even be congenital. This craniomalacia usually spares the frontal bones, affecting by predilection the occipital, the parietal, and the petrous portions of the temporal bones; it is the soft occiput—*weiche Hinterkopf*—the craniotabes of Elsässer (Stuttgart, 1843).

Elsässer attaches a tragic significance to this cranial lesion. Struck by the occipital softening he was led to dread pressure on the brain, and he attributed to this softened occiput the convulsions which often terminated the life of the wretched little patients whom he observed. Of twenty-nine cases fourteen died, ten of these in convulsions. However, when we search for craniotabes systematically in children during the first years of life it is surprising with what frequency we encounter it even in apparently healthy children who do not seem to be rachitic or predisposed to rickets. Syphilis, which was regarded as a cause of the condition by Parrot, has nothing to do with the production of craniotabes.

Although this lesion does not seem to play any pathogenic rôle of consequence, and although it is responsible neither for laryngeal spasm nor for convulsions, nor yet for tetany, in the production of which Kassowitz regarded it as active, it nevertheless deserves a brief description. Craniotabes is a silent and latent symptom and must be searched for. The hand pressed lightly over the skull encounters softened, depressible spots in the posterior part. The sensation is

as if the bone were less hard, yielding to the finger like a piece of cardboard, of parchment, or of mica. In extreme cases the finger is separated from the brain substance merely by a soft and flexible fibrous membrane. Sometimes the softening is of wide extent, involving a large part of almost all of one or several bones, while sometimes it is limited to a small area, the resulting depressions scarcely admitting the extremity of one finger. Pressure on these softened spots is well borne by the child, and the danger of compression of the brain in this condition is almost entirely imaginary. I have seen very many children affected with craniotabes; some (very few) had convulsions or laryngismus stridulus, but most of them had never had even the slightest nervous symptoms. On the other hand, I have often seen children suffering with glottic spasm who were wholly free from craniotabes.

Craniotabes develops slowly and is always cured upon the renewal of the process of ossification. It is encountered in badly nourished children, those brought up on the bottle or who receive an insufficiency of breast milk, in twins, and in short, in all who do not obtain enough food of the proper quality. It is especially frequent between the ages of six and eight months, but may be observed both before and after this age, from that of a few weeks up to twenty, twenty-two, or twenty-four months. We must differentiate craniotabes from congenital or traumatic fissures of the skull and from loss of substance with meningocele, due ordinarily to a traumatism followed by resorption of the bone.

Next to the cranial vault, rachitis may impress its marks upon the face. Fleischmann has shown that the inferior maxilla may acquire a polygonal form which will interfere with the evolution of the permanent teeth. The palatine vault may be deformed, the alveolar border may be projected forward; the nasal fossæ will be narrowed in consequence, the tonsils will be approximated to each other, and there will be a marked predisposition to coryza and catarrhal sore throat.

These lesions, however, are rare. The most common effect of rickets is seen in the retardation of the first dentition. A healthy child cuts his first tooth at the age of six, seven, or eight months; a rachitic infant will have no teeth before the twelfth or fifteenth month. If the disease has commenced after the eruption of the first teeth, the appearance of the others will be delayed, and the child, who ought to have his twenty teeth at two or two and a half years of age, will not have all of them before the end of the third or fourth year. Along with this delay in dentition there may be a precocious caries of the milk teeth. When the jaws are deformed the permanent teeth may

overlap each other, presenting an irregular implantation. These symptoms just enumerated are the cephalic manifestations of rachitis, often the first in point of time.

Thorax.—The normal curves of the clavicle are often exaggerated, its regular arcs being transformed into acute angles, whence results a shortening of the bones and a consequent narrowing of the shoulders.

The ribs present two kinds of deformities, inflections and nodosities. Fastened between two vertical pieces, the sternum and the vertebral column, the ribs yield to atmospheric pressure and the action of the diaphragm and are depressed laterally, driving in the lungs, pushing back the heart, narrowing the thoracic cage, pushing the vertebræ backwards and the sternum forwards (chicken breast, pectus carinatum). This lateral sinking-in of the ribs affects only the middle ones; the upper ribs, which are short and protected by thick muscles, do not become deformed; and the lower ones, which are more movable and more free from attachments spread out over the abdominal viscera. On transverse section the thorax, with its lateral indentations and its anterior and posterior projections, presents the form of a figure 8. We may readily understand that the play of the lungs and of the heart will be interfered with by a deformity of this nature. Some patients have a sinking-in of the sternum, either longitudinal or funnel-shaped. Among the most curious and best defined of the rachitic manifestations are the nodosities at the junction of the ribs with their cartilages, forming the "rachitic rosary;" these nodosities project inwards as well as outwards as may readily be observed at autopsies. The vertebral column often escapes. When it is affected there is a large rounded kyphosis in the dorsal region, a wider and more projecting and less angular gibbosity than that of Pott's disease. In late childhood and adolescence the deformity observed is scoliosis.

Pelvis.—The deformities of the pelvic bones may have grave consequences in women; the sacrovertebral angle being more projecting, the pelvis is narrowed and natural labor is rendered difficult, sometimes even impossible.

Extremities.—It is in the extremities that the rachitic deformities are most striking and characteristic by reason of the curvatures of the bones, the swelling of the epiphyses, and the resulting diminution in height.

The epiphyseal swellings are especially noticeable at the wrists and ankles. The radiocarpal and the tibiotarsal articulations are surmounted by a sort of prominent ring or bracelet caused by the increase in size of the epiphyses. The swelling is hard, painless, without inflammatory symptoms. The neighboring articulations seem to be relaxed and movement of them is sometimes accompanied by a crack-

ing sound. These epiphyseal swellings are an early manifestation of the disease; they precede the curvatures of the shafts of the bones and they also disappear before them. All the long bones of the extremities—femur, humerus, tibia, fibula, ulna, radius—may present curvatures or fractures of their diaphyses. In general the curvatures are in the direction of the natural curves; the normal concavity of the radius and of the ulna is increased, the torsion of the humerus is accentuated, the femur projects outwards and forwards, describing with its fellow an imperfect oval. The curvatures of the legs are symmetrical or unequal; sometimes the two tibiæ present to each other a concave surface, forming parentheses—( )—the child is bandy-legged; sometimes their convex surfaces look towards each other—)(—the knees incline towards each other and knock together, while the feet are divergent—the child is knock-kneed (genu valgum). Double genu valgum, combined with the femoral oval, gives to the lower extremities an X-shape. If the curves are not symmetrical we may have one member straight while the other is angular, the two having the shape of a K; this figure is represented by unilateral genu valgum, due to swelling of the internal condyle of one femur. Some patients, during early childhood or later, have adduction with external rotation of the lower extremity, caused by a flexion of the neck of the femur, which, instead of forming with the diaphysis an angle of 126° to 128°, makes one of 100°, of 80°, or of 60°. This is called coxa vara; it is distinguished from hip disease by the absence of any articular lesion, ankylosis, etc.

The tibia may be deformed by multiple subperiosteal fractures, which make its crest irregular and angular. When it is not fractured it presents the characteristic sword-blade inflection; its crest forms a regular, rounded, forward projection, its posterior border forms an arch, its lateral faces are flattened; the whole bone is smooth and without roughened surfaces or exostoses.

When the disease is very severe these lesions are incurable and permanent, development is impeded, the stature is diminished, and the patients are condemned to remain dwarfs throughout life. In some cases the deformities grow less marked though the dwarfish stature persists.

The general appearance of a rachitic child is as follows: if the child is stripped naked and observed from the front, one is struck by the volume of his head and belly, joined by a straight body, the whole recalling a figure-of-8 or a gourd. The sternum projects forwards, the spinal column is curved backwards, the ribs are depressed laterally, separated below, and marked by a double symmetrical rachitic rosary. Add to this that the wrists are doubled in size, the

forearms are curved inwards, and the legs are shortened, separated, and bent in various directions, and you will have a never-to-be-forgotten aspect of a rachitic child at rest. If he walks, when that is possible, he does so with difficulty, waddling like a web-footed bird; he has a duck's gait. Some children have only certain extremities, sometimes but one, deformed; these are said to suffer from partial rickets.

We may distinguish several forms and degrees of rachitis. The disease may be slight, only suggested as it were, declaring itself merely by a delay in learning to walk, in the eruption of the teeth, in the closure of the fontanelles, and by a certain softness and flaccidity of the muscles; but there are no bony deformities and the patient may recover without any curvatures or epiphyseal swellings.

Alongside of these mild cases, which are very frequent and readily curable, we find cases of moderate severity with noticeable but remediable deformities. Then come severe forms belonging to surgical rachitis. In these the skeleton is markedly deformed, there is a notable loss of power, and the general condition is bad. Hygienic and medical treatment will not suffice for these cases, we must have recourse to surgical and orthopedic measures.

In all these forms, alongside of the objective lesions of the bones, we find more or less marked visceral symptoms. The general nutrition is perverted, but not always in the same sense; for we see not only thin, pale, and cachectic children with rachitis, but we also see those who are large, florid, and in good flesh. In all these cases, however, the performance of the digestive functions leaves much to be desired; the appetite may be diminished, increased, or irregular; there may be diarrhœa or constipation or alternations of the two; sometimes there is vomiting—in a word, we have the symptoms of dyspepsia. There is marked loss of power; the child lies heavily in the arms of its nurse, it cannot sustain the weight of its head or of its body; if it is able to walk it frequently stops, refusing to go further, and sinks down on to the floor. It becomes cross, bad-tempered, its whole character changes; sleep is disturbed; the face is covered with sweat. There seems to be a little fever with evening exacerbations, and the pulse is accelerated.

The intelligence may or may not undergo change. It has been said that rachitic children are more intelligent than others, but it is impossible that rachitis should influence favorably the development of the brain. Although the disease usually spares the intellectual faculties, it may in some cases retard speech, benumb the thought, and induce a condition approaching idiocy.

The course of the disease is slow and progressive, its development taking months and years. Sometimes rachitis appears to be ar-

rested in its evolution and even to recede; but let an acute affection intervene or an accident or some other hygienic or morbid condition, depressing the patient's strength, and the ground gained will be lost again. We must, therefore, preserve these little patients against the causes of aggravation or of recurrence.

Alongside of the ordinary chronic forms an acute variety of rachitis has been described, astonishing in the suddenness of its onset and in the rapidity of its progress. We may see children fall in the course of a few days or weeks into a disquieting condition of marasmus and of cachexia; they cry when they are taken up, they can neither stand alone nor move their extremities, appearing as if paralyzed; in examining them closely we notice a swelling of certain epiphyses, an intraperiosteal exudation, articular pains, fever, depression, anæmia; the gums, when the child has any teeth, are fungous and bleeding, the eyelids are swollen and ecchymotic, and the eyeballs are sometimes projecting. In the presence of such a sombre collection of symptoms the physician naturally thinks of an infectious disease, of an osteomyelitis, rheumatism, or septicæmia. This is what has been described under the name of acute rachitis. The condition may indeed coincide with rachitis, but it is an independent affection that has been described as infantile scorbutus by Barlow, Northrup, and others.

Prognosis.

The prognosis of rachitis depends upon the form and the severity of the disease. Mild forms are cured rather promptly without complications and without difficulty, provided that the significance of their symptoms be understood and that their causes be recognized, and consequently be removed by change in diet and in general hygiene. The moderately severe forms are also curable, but less rapidly; a period of three, four, or six months is necessary to affect a cure of moderately severe rickets. When the disease is partial, when the deformity is restricted to one member (genu valgum), to the head (craniotabes), or to the trunk (scoliosis or kyphosis), the termination is hardly more rapid than in the generalized forms. The intensity and the depth of the lesions are more important than their extent or their dissemination. The more the process of ossification is disturbed the slower is the cure. Often even partial rachitis does not yield to medical treatment alone and the assistance of the surgeon must be obtained.

The severe forms with excessive deformities yield very slowly to treament, too often, indeed, incompletely, leaving curvatures which cannot be overcome without the intervention of the surgeon.

But rachitis is not a fatal disease, it does not directly compromise existence. Relatively good, therefore, *quoad vitam*, the prognosis is bad as regards the duration of certain visceral manifestations of the dyspepsia, which, having preceded the bony lesions, survives them. This rachitic dyspepsia is the more marked and persistent in proportion as the rachitis itself is more pronounced. In mild cases the gastric symptoms are slight.

In the female sex the prognosis is more grave because of the deformity of the pelvis, a much-feared cause of dystocia, which may necessitate symphyseotomy, cephalotripsy, Cæsarean section, or other obstetrical operations more or less dangerous for both mother and child. I have seen an unfortunate woman with narrowed pelvis as the result of rickets, seven of whose eight successive pregnancies resulted in stillbirth by reason of vicious presentation, length of labor, and tractions made upon the child. One child was born apparently dead like the others, but was resuscitated after an hour's insufflation. This eighth child was indeed snatched from death, but his arms were so stretched during birth that he has a permanent double paralysis of the brachial plexus, and is necessarily an invalid for life.

Complications.

The complications of rachitis are numerous and various; they belong, however, only to the severe and well-marked cases of the disease, and mild cases seldom present any complications. We shall study successively the complications on the side of the bones and of the locomotor apparatus in general, of the digestive apparatus, of the respiratory organs, of the circulatory system, of the nerves, and of the skin, not neglecting more extensive dyscrasiæ, such as anæmia, leucocythæmia, scurvy, scrofula, and obesity, and the infectious diseases, such as whooping-cough, influenza, pneumonia, etc., which are aggravated by a preëxistent rachitis.

Locomotor Apparatus.—The fragility of the bones exposes rachitic subjects to fractures, complete or incomplete, single or multiple, of the extremities, and sometimes of the clavicles. These fractures are spontaneous, muscular action alone sufficing to produce them, or else are provoked by insignificant injuries which would have no effect upon healthy bones. For this reason it is advisable not to let patients who are profoundly affected with rachitis try to walk. Some children present at the time of birth multiple fractures which are attributed to fœtal rachitis. Sometimes consolidation occurs rapidly even with an excessive amount of callus; sometimes it does not occur at all and a pseudarthrosis results. The insidious occurrence of these

fractures often leads to their non-recognition, so that they are not reduced and are then active causes of angular deviation. They are often subperiosteal, not accompanied by any abnormal mobility and consequently not attracting any attention.

The wrist and ankle joints are often deformed, their ligaments are relaxed and elongated, the result of which is an abnormal mobility which interferes with the articular functions and predisposes to arthropathy. Sometimes there is a cracking sound heard on motion in the elbow joints, the wrists, etc. In one child whom I have seen the elbow could not be extended, it was ankylosed; in another the bones were sensitive, suggesting a comparison with growing pains.

Bony torticollis, late genu valgum, and painful flatfoot may often be regarded as complications of rickets. Some patients present muscular atrophy and a loss of power in consequence of the prolonged immobility to which they have been subjected. I may finally mention, among the rare complications, exostoses of the tibiæ which I have observed in a little girl of twenty-seven months. This child, in addition to various rachitic deformities, notably a left genu valgum, presented on each side of the superior tibial epiphysis prominent angular symmetrical exostoses, similar to the exostoses of growth.

Digestive Apparatus.—These complications are very frequent. The sometimes enormous enlargement of the abdomen of rachitic children is well known. This big belly is usual at the beginning of the disease; it is due neither to deformity of the thorax nor to a pushing down of the diaphragm, nor, again, to enlargement of the mesenteric glands or of the liver. It results most commonly from dilatation of the stomach. Rachitic children, indeed, are polyphagic and polydipsic, their appetite is insatiable, and they constantly overload the stomach. Later the appetite diminishes or disappears, but the thirst persists and the excessive consumption of liquids maintains and even increases the dilatation of the stomach. This gastric ectasia, to which I have called special attention (*Archives de Médecine*, 1884), is very common if not constant in rachitic children. It plays a rôle in the production of Glisson's disease; it survives the osseous deformities which it has frequently preceded and which it accompanies, and it carries with it a long-continued or permanent dyspepsia.

The intestine also is dilated throughout its whole extent, from which result a relaxation of the abdomen and eventration, a tendency to umbilical and inguinal hernia and to prolapse of the rectum, the frequency of which I have noted in rachitic conditions. The complications are chronic and long continued, and the bony lesions are cured sooner than those of the digestive tube, the dyspepsia being found at all periods—in childhood, in adult life, and even in old age.

Upon this dyspepsia, which is sometimes latent and endurable, are engrafted acute attacks, more or less severe enteritis, indigestion, vomiting, lienteric or infectious diarrhœa, complications which are to be dreaded especially in summer and which may take the life of the little patient. The adnexa of the digestive tube, especially the liver, suffer in consequence of the gastro-intestinal lesion. Hypertrophy of the liver is frequent, catarrhal jaundice is not rare, and amyloid degeneration of this viscus is possible. Finally, in severe cases accompanied by cachexia there may be ascites.

Respiratory Apparatus.—The complications on the side of the respiratory organs are produced in two ways: 1. Sometimes they are the result of compression exercised upon the lungs by the falling-in of the ribs; the thoracic cage is narrowed, and as a result there is emphysema in certain parts of the lungs and congestion in other parts, with a constant tendency to bronchial catarrh, etc. 2. Sometimes they are subordinate to the digestive troubles and arise from auto-intoxication. It is thus that we are to explain the chronic or recurrent attacks of sibilant bronchitis in these big-bellied children, and the attacks of dyspeptic asthma observed in them. These two influences combined—viz., thoracic deformity and gastro-intestinal auto-intoxication—render attacks of bronchitis and bronchopneumonia frequent and of grave import in rachitic individuals. They also predispose to tuberculosis through impairment of the functional action of the lungs and oxygenation of the blood. We very often see in children's hospitals rachitic patients attacked by grave pulmonary troubles with rapidly fatal issue to which healthy patients would be much less exposed.

Circulatory Apparatus.—The complications affecting the organs of circulation are of a mechanical nature and are observed only in cases of excessive deformity of the chest. The heart, crowded to one side, compressed and impeded in its movement, contracts rapidly and irregularly, and we see palpitation, tachycardia, and arhythmia; sometimes there is hypertrophy of the organ. We may find at autopsy milk spots on its pericardial investment, the evidences of compression exercised by the deformed bones. But these affections are rare.

Nervous System.—Much more common than the preceding are complicating affections of the nervous system. In the first rank of these figure general or partial, external or internal convulsions. General convulsions (infantile eclampsia) are not rare, a fact which need not astonish those who know the rôle played by digestion in these accidents. Whether reflex or toxic these convulsions have very frequently their point of departure in the digestive tube. All au-

thors have insisted upon the frequency of convulsions in rachitis, especially when the disease is well marked. It has been held that the convulsions were associated with rickets of the skull, craniomalacia or craniotabes of Elsässer, but this is not so, for we may see convulsions indifferently in children who have cranial lesions and in those who have none. We have to admit a general nervous hyperexcitability in rachitics which would explain the occurrence of convulsions, or else an auto-intoxication, originating in the digestive tube, which provokes the attacks.

As to internal convulsions, glottic spasm, laryngismus stridulus, which some writers have believed to be especially under the dominion of craniotabes, I believe that they are in no wise dependent upon it, but that their pathogenesis is the same as that of eclampsia.

Tetany itself, which is so rare in its complete manifestations, is a neurosis of a toxic nature which we must also refer to the common digestive troubles of rachitic children.

An improvement in the nutrition, treatment of the intestinal and stomach troubles, and the neutralizing of the poisons formed in these organs are the means for the prevention or cure of all these nervous manifestations, of which the frequency has been exaggerated and the pathogenesis unrecognized in rachitis. Craniotabes is so little the direct cause of convulsions that we often see the latter present when this condition is absent, and vice versa; there is, therefore, no pathogenic relation whatsoever between these two conditions.

Rachitic children frequently suffer from night terrors; they awake from slumber with a start, crying out and not recognizing those about them. These, like the other nervous complications, are dependent upon the digestive troubles; we know indeed that a simple indigestion may provoke them in nervous children. They may be prevented by appropriate regimen.

We are sometimes struck by the weakness of the nervous system, which, even when the limbs are fairly straight and the muscles powerful, results in a loss of power closely approaching paralysis. There is a sort of rachitic pseudoparalysis which calls for electrical treatment for its relief.

On the side of the brain we ought to mention the possibility of hydrocephalus which sometimes complicates rachitis, mingling its symptoms with those of the craniomalacia. The resemblance between hydrocephalics and rachitics is sometimes very striking; there are the same large head, open fontanelles, united sutures, etc.

Finally, as to the intellectual qualities: Although many rachitic children are intelligent, observant, and alert, some are apathetic, inert, and imbecile, or even idiotic; they speak slowly and with

difficulty, and their intellectual faculties do not expand. All functions of relation are retarded in them—walking, speech, the special senses of hearing and of sight, etc. They are laggards.

Cutaneous System.—The skin of rachitic children is generally healthy, white, and of normal color and consistence. However, it is not rare to see, either before the occurrence of deformities or during or after this stage, various eruptions, usually papular and pruriginous. Thus we see acute, subacute, recurring, or chronic urticaria, which bears witness to defective functional action of the digestive apparatus. Then we have pruriginous strophulus, very common in badly nourished babies, characterized by an eruption of discrete papules, sometimes surmounted by vesicles. Then, again, there may be prurigo, the little rounded acuminate papules of which are frequently torn through scratching and converted into little crusts of dried blood. All these eruptions, ordinarily temporary only, may last indefinitely in some cases and pass into a chronic prurigo, the prurigo of Hebra, an almost incurable affection, the origin of which goes back frequently to the early years of life.

Rachitic children are also exposed, as a consequence of their defective alimentary hygiene and habitual dyspepsia, to moist eruptions, to eczema of the face or of the genitals, to impetigo, or to ecthyma, which may leave cicatrices on the buttocks and sacral region that must not be confounded with lesions of hereditary syphilis.

All those children whose skin is irritated by scratching will have more or less enlarged glands, the adenitis sometimes resulting in suppuration.

Still other cutaneous complications may be observed. In one case, that of a little girl of seven years who was profoundly rachitic, having a height of only 80 cm. (two feet ten inches), I once saw a remarkable cyanosis of the feet—local asphyxia of the extremities.

The Blood.—Simple anæmia is not rare in rachitic children who have suffered much and who have lived under unfavorable hygienic conditions. Auscultation will reveal in such children a systolic murmur at the base with propagation into the vessels of the neck. It is also in these anæmic rachitics that we sometimes hear a systolic murmur, analogous to the carotid souffle, in auscultating the anterior fontanelle (H. Roger). These children are pale, weak, flabby, breathless on the slightest effort; some are thin, others in good flesh; all have deformed and softened bones incapable of supporting the weight of the body. The anæmia of rickets may be complicated with hypertrophy of the spleen. Acute splenic anæmia has been well studied by Carr, Colcott Fox, Luzet, and others. The red corpuscles are less numerous than in health, the white are more abundant, and nu-

cleated red corpuscles are present in the blood. Arsenic, cod-liver oil, and iodide of iron may be given in these cases.

I have already spoken of scorbutus, another blood disease, which may complicate rachitis and which will disappear upon the institution of proper hygienic treatment.

Infectious Diseases.—When an infectious disease, such as measles, diphtheria, scarlet fever, whooping-cough, typhoid fever, influenza, or tuberculosis, attacks a rachitic patient it is of much greater gravity than when affecting a healthy child.

Whooping-cough, by reason of the violence of its spasmodic attacks, threatens the life of the rachitic child with deformed thorax, disposing to asystole. Of itself rickets is a curable affection, but when complicated by a general infectious disease it is often fatal, the termination of such diseases depending in very great measure upon the soil in which they are engrafted; rachitis offers a soil favorable to the growth of pathogenic organisms.

Tuberculosis carries off a certain number of children suffering with rachitis. It may be met with among them in any of its usual localizations (lungs, ganglia, bones, articulations, meninges, skin, etc.). Hereditary syphilis is another aggravating cause which weighs heavily upon rachitic children. Scrofula is less serious, and we often see rachitics suffering with otorrhœa, blepharo-conjunctivitis, keratitis, or ozæna who recover perfectly.

Diagnosis.

When rickets presents its usual bony deformities, curves, and epiphyseal swellings, it is very easy of recognition, the diagnosis being self-evident; but attention is often required to unmask the attenuated forms, the initial stages, and the partial forms, limited to one member or one bone.

A child, previously in good health, develops weakness, malaise, and pallor; it is less lively than usual, sinks down in the arms of its nurse, and refuses to stand; it is tired, inert, without rebound, and without energy. If with these symptoms we note that its alimentation leaves much to be desired, that the eruption of its teeth is delayed, and that the anterior fontanelle does not close, we have to fear the onset of rachitis. In every poorly nourished child, either bottle-fed or prematurely weaned, rachitis is imminent and we ought to be on the watch to seize the first premonitory signs of the trouble. These signs, it is true, may be fleeting and the disease may become arrested in its progress, recede, and disappear; but an attentive and intelligent observer will not be deceived. We must then be able to recognize

the slight forms of rachitis in order to attack them early and save the child from the severe troubles which would not fail to arise if the malady remained unrecognized. The disease progresses but slowly, and we have time to fight against the general invasion of the system.

When rachitis is partial, limited to one member or one bone, the diagnosis may present real difficulties. Given a deformity of the vertebral column, a gibbosity of short radius, with weakness of the lower extremities, which are, however, straight, the rest of the skeleton also appearing to be normal—are we in presence of a rachitic kyphosis, or of Pott's disease? If the kyphosis is frankly angular Pott's disease is evident, the projection of a vertebra backwards bearing witness to the destruction of the vertebral bodies. The rachitic gibbosity has a long radius, it is rounded and not angular. But there are cases in which doubt is admissible and in which we must examine the spinal column with the greatest care, study its degree of mobility, palpate and percuss the spinal processes and the lateral depressions, and investigate the sensibility and motility of the lower extremities. In cases of doubt the diagnosis should be reserved until another examination can be made at a later period.

The lateral deviation of the spinal column, scoliosis, can scarcely be confounded with Pott's disease. I have seen a girl of fourteen years with a right lateral curvature of such an extent that the thorax was dreadfully deformed and respiration and also locomotion were interfered with. This child had had whooping-cough at eighteen months and typhoid fever at seven years; she had been rachitic. May the lateral curvature of adolescence be due to a partial rachitis of late origin? There is a tendency to-day to reply in the affirmative, since we know that rachitis disturbs profoundly and for a long period the process of ossification and that cartilaginous islets may persist in the substance of apparently perfectly healthy bones. The same may be said of unilateral or bilateral knock-knee which in early childhood is distinctly rachitic, but which in later life might have another origin. However, the downward projection of the internal condyle of the femur, which characterizes genu valgum, seems always to depend upon rickets.

The deformities of the spinal column (kyphosis), of the ribs, and of the extremities, which make their first appearance in adult life belong rather to osteomalacia than to rachitis—two affections which are distinguished especially by the age of the patient, having in other respects many resemblances one to the other.

Congenital dislocation of the hip may be mistaken for rickets, the children affected with it walking with the knees turned in (knock-kneed). But it will suffice to search for the head of the femur in

order to determine that it does not occupy its ordinary position, but is in the external iliac fossa above the cotyloid cavity, and thus establish the diagnosis. We must not forget, however, that rachitis may coexist with congenital dislocation of the hip, as also with Pott's disease, and we must be able to distinguish the symptoms belonging to each. I have seen a little girl, seven and a half years old, who was bottle-fed and did not walk until she was eighteen months old, who suffered at the same time from rachitis and from double dislocation of the hip. The abdomen was enormous, the forward curve in the lumbar region was excessive, and walking was very difficult.

When a child does not begin to walk until late or walks badly we think immediately, and usually with reason, of rachitis. However, walking may be retarded or prevented by other causes, by atrophic infantile paralysis, which may be recognized by its characteristic course, by its localization in certain groups of muscles, and by the accompanying atrophy of these muscles. Walking may also be retarded or prevented by syphilitic pseudoparalysis or by obstetrical paralysis.

When rickets is limited to the lower extremities, to the tibiæ or to a single tibia, we must distinguish it from hereditary syphilis of the bones, the characteristics of which have been well described in France by Fournier, Lannelongue, and others. The syphilitic tibia, called also the Lannelongue tibia, is a bone which appears to be curved, but which is simply swollen, nodulated, of uneven surface, deformed by gummatous deposits, osteophytic layers, etc. The rachitic tibia, on the contrary, is convex anteriorly, concave posteriorly, flattened laterally, and actually curved; it has the shape of a cavalry sabre. In addition to these objective symptoms, which are sufficient for a diagnosis, we may have stigmata on the part of the eyes, of the ears, and of the teeth (Hutchinson's triad), and also of the integuments, which will betray hereditary syphilis.

When rachitis is limited to the head we may think of hydrocephalus, a congenital disease characterized by an extraordinary development of the cranium, by a widening of the sutures and of the fontanelles, by idiocy, etc. In hydrocephalus the cephalic souffle is rarely perceived on auscultation of the anterior fontanelle, the extremities are not deformed, and the face contrasts by its smallness with the monstrous enlargement of the cranium. Rickets, may, however, be complicated with a certain degree of hydrocephalus, which may be recognized by the large size of the skull, the widening of the fontanelles, and occasionally by the presence of craniotabes.

Cranial rachitis appears to be more precocious than that of the extremities. It is without doubt the first in time of appearance, and many physicians do not wait for the appearance of curvatures

of the bones and swelling of the epiphyses in order to establish the diagnosis. It is sufficient for them to recognize the abnormal widening of the fontanelles or an unusual softening of the occipital bone or its neighbors to pronounce the disease rachitis. Without doubt craniotabes may be due to rickets, but we must remember that it is frequently met with in children who are apparently healthy and who are not destined to present any other rachitic lesions.

Etiology and Pathogenesis.

Rachitis, a disease of misery, is especially frequent in cities, in the large industrial centres, and in quarters inhabited by a dense population, poor and badly nourished, among whom the children are destined to an unhealthy or insufficient alimentation, to artificial feeding, and to early weaning, the mothers being obliged too often to leave their homes to go to the shops and the factories to gain a meagre pittance for the family. According to Pini, of Milan, the families of the concièrges, living in narrow and dark apartments and on insufficient wages, furnish the greatest proportion of rachitics (964 out of 4,176). In America the colonies of Italians, of Irish, and of Germans present numerous cases of rickets, because their members are poor and badly lodged. The negro race is not exempt in American cities. We have here to do with a matter not of race but of hygiene, and especially of alimentary hygiene.

If the mother is able to nurse her infant and give to it all the care which its age demands it will not become rachitic; but separate these two beings who are made to be closely united, give the child to mercenaries living at a distance and secure from surveillance, replace the breast by the bottle, and you will almost surely provoke rickets. Where the bottle is unknown, where infant feeding is always from the breast, there rachitis is absent. It is frequent under the opposite conditions.

Next after artificial feeding comes suckling by a poor nurse, one whose milk is too old, indigestible, or which contains too large a proportion of casein; then irregular times of nursing, and finally a delay in weaning and in the admission of solid food to the infant's diet at a suitable period. When a woman nurses twins she can very rarely do so with justice to both children, and the infants are apt to suffer from rachitis.

But indigestion and over-feeding are more often at fault than are a diminished supply of food and inanition. Mothers sin more often by excess than by deprivation, and they are only too apt to gorge their infants with food unsuited to their age.

Much has been said of heredity in rickets, and the number of rachitic children in the same family and the occurrence of congenital rickets, lend plausibility to the theory of heredity. But if we will investigate the hygienic conditions of these cases of apparently inherited rachitis we shall find in many instances that it is not the germ of the disease that is inherited, but rather the unhygienic habits that are transmitted from parent to child. It is indeed not uncommon to see a woman who has been rachitic give birth to children entirely free from any evidences of the disease and who will surely escape it if they are well nourished. We may say, therefore, that there is no direct inheritance of rachitis; but it may readily be conceived that children who are the issue of weak, delicate parents, of those who are too old or ill (tuberculous or syphilitic) will be predisposed to rickets. It is therefore in this restricted sense that we are to regard rachitis as hereditary. Out of 4,176 cases, Pini found but 52 which were apparently hereditary; in 86 instances he found consanguinity in the parents, but other causes of the disease coexisted. The argument from the number of cases in one house is no more in favor of the hereditary nature of rachitis than it is of its contagious nature.

Fœtal rickets, with its deformities, its multiple fractures, its anomalies of ossification, presents a number of unrelated phenomena which do not all by any means belong to true rachitis. One is not born rachitic, one becomes so. The fact of the acquired origin of rickets is confirmed experimentally; domestic animals (pigs, calves, puppies) become rickety when their alimentation is defective. Wild animals in a captive state (lions, monkeys, etc.) are also exposed to the danger of rachitis when the mother's milk is replaced by a too nitrogenous alimentation. Young chickens and pheasants may also become rachitic when improperly fed.

Dr. Cheadle believes that it is especially the giving of starchy foods too early that predisposes to rickets, and he advises the use of animal fats as a prophylactic measure. At the London Zoological Gardens the young bears fed on biscuits and rice, the monkeys fed on vegetables, and the young lions fed on meat all became rachitic. Sutton had them fed with pap made of milk, and they all recovered in three months.

It is said that girls are more prone to become rachitic than boys, but a study of statistics of over two thousand cases does not bear out this assertion.

The question of age is more important. If we except the rare conditions of congenital rickets and of the rachitis of adolescence, we may say that rachitis is a disease of the first two years of life. It begins at about the tenth or twelfth month, and may arise as late as

eighteen months or two years, but it almost never begins after the third year of life. It is a disease, as regards time of origin, of the first dentition. Out of 1,662 patients in whom the age was noted, 1,268 were between one and two years old. Pini found 2,974 children two years of age out of 4,176 cases examined, and it will thus be seen that his statistics confirm mine.

Hereditary syphilis, which Parrot regarded as the cause of rickets, appears earlier than the latter, being often intrauterine. Parrot's arguments for this causation are that the osteophytes and the spongy osseous tissue are common to hereditary syphilis and to rachitis, but there is nothing specific in these lesions. As to the pretended stigmata, the cicatrices of the buttocks, the lingual desquamation, the erosions of the teeth, and the natiform cranium, they are met with as well in non-syphilitic as in syphilitic children. More than this, the statistics of all pediatric physicians, in America as well as in Europe, bear witness against this theory of Parrot's. Syphilis is at least as common among the rich as among the poor, but rickets is a disease of the poor, and is very rarely met with among the well-to-do classes of the community. Syphilitic parents have been seen to have healthy children, and the children of parents who were certainly free from syphilitic taint have been rachitic. In many cases, furthermore, in which syphilis in the parents has been seen to coexist with rachitis in the children, inquiry has shown that the disease of the parents was acquired subsequent to the birth of the children and the appearance in them of rickets. No doubt rachitis is not rare in hereditary syphilitics, as it is in all children who are weakened by any disease whatever, but the influence of the syphilis is not specific or direct; it is very simple and of dystrophic nature.

Let us see how the most ordinary cause of rickets—namely, vicious alimentation—acts. The cause is evident but the pathogeny is obscure.

Gamba holds that there is phospho-calcareous inanition; the lime salts are deficient either in consequence of insufficient supply or because of defective assimilation (through some intercurrent dyspepsia). We have seen that over-feeding of young children is more common than a deficient supply of food. Therefore if phosphate of lime is ingested in sufficient quantity we must blame the gastro-intestinal dyspepsia as impeding its perfect utilization. Pini remarks that diarrhœa figures among the prodromes of rachitis. Others regard constipation, vomiting, alternations of diarrhœa and constipation, borborygmi, enlarged abdomen, etc., as premonitory symptoms.

Cow's milk, which serves for the nourishment of most children deprived of the breast, is rather rich in lime salts, but it is indigestible

and almost always provokes more or less gastro-intestinal disturbance in babies. There is an abundant non-utilizable residue, and the child, in order to meet his wants, is obliged to ingest an enormous quantity which distends the stomach, exhausts the intestine, irritates the mucous membrane, and induces chronic dyspepsia. I showed in 1884 (*Archives de Médecine*) that dilatation of the stomach was very common in rachitic children and that this dilatation persisted even after the subsidence of the osseous deformities which it had contributed to produce by interfering with the assimilation of lime salts or by favoring the absorption of bone by the acid materials which it threw into the circulation. In rachitis resulting from dyspepsia due to improper feeding the loss of lime material by the bones is greater than the assimilation, and the disturbance of nutrition finds its expression in phosphaturia.

We do not know yet whether this decalcification of the bones is due to lactic acid, to acetic acid, or to some other principle; but it is the consequence of digestive troubles, as was shown by the experiments of J. Guérin upon dogs (1838), of Chossat on pigeons, of Roloff on young horses, etc. Baginsky having submitted animals to calcareous inanition and to absorption of lactic acid rendered them rachitic, and Heitzmann obtained the same results; Ritter also believes in the presence of lactic acid and in its solvent action upon the bones. Kassowitz declares that phosphorus which in small dose cures the disease, in larger doses would cause it. But this chemical solvent action of acids which is invoked in the explanation of the pathogenesis of the disease, although it might explain the facts of decalcification and of softening of bone, does not take into account the swelling of the epiphyses. May not the latter be the result of an irritative process, of a mild parenchymatous osteitis (Virchow, Kassowitz)?

In conclusion we will enumerate briefly the chief pathogenic theories:

1. *Parrot's Theory:* Rachitis is always of syphilitic origin, and is never due to faulty alimentation.

2. *The Nervous Theory of Pommer and Tedeschi:* Rachitis is a trophic affection of the bones, brought about through the influence of the central nervous system.

3. *Infectious Theory:* Rachitis is a contagious disease (Chaumier); it is of microparasitic origin (Mircoli).

4. *Alimentary Theory:* Rachitis is a disease of nutrition occasioned by faulty alimentary hygiene (Glisson, J. L. Petit, J. Guérin, Trousseau, Chossat, Roloff, Gamba, Fonssagrives, Cheadle, and others).

5. *Modified Alimentary Theory:* Rachitis the result of faulty ali-

mentation and is preceded by digestive troubles, chronic dyspepsia, dilatation of the stomach, or enteritis, which profoundly disturb the process of assimilation of lime salts and favor the decalcification of the bones (Jacobi, Heitzmann, Bouchard, Baginsky, Comby, and others).

Prophylaxis.

The preventive treatment of rachitis borrows all its measures from hygiene. If we could insure the breast-feeding of all young children rickets would disappear, or at least would become very exceptional. Unfortunately its principal cause, poverty, escapes the physician's power to remedy. It is impossible to prevent women without means, workwomen who have only their wages to live upon, from taking their children from the breast and feeding them artificially.

When rickets is the fruit of ignorance we can accomplish more. We must teach the mothers and all those who have the care of children the rules for feeding babies, the comparative infrequency of nursing (six or eight times in the twenty-four hours), late weaning, supplementary alimentation towards the eighth month, choice of foods, etc. When a child is fed artificially, or when the breast milk is supplemented by other food, the risks are greater and the precautions ought to be more scrupulous. The nursing bottle should have no tube, it should be kept scrupulously clean, the milk should be sterilized, etc.

Weaning should be carefully regulated; it ought never to be sudden but should be prepared for some time in advance. The number of times the child is put to the breast should be gradually diminished while at the same time the supplementary feeding should be increased.

Next to alimentation prophylaxis demands the carrying out of other hygienic conditions. The clothes of the child should be warm, the living apartments healthy, that is to say dry, well ventilated, and sunny; the body should be kept clean, the child should be taken into the open air frequently, etc. The prophylaxis of rachitis is therefore purely a question of infantile hygiene.

Treatment.

If we appeal to hygiene in order to prevent rachitis, we ought equally not to neglect hygienic measures in order to combat it when it is declared. Fresh air, a residence in the country, and salubrious apartments act by improving nutrition, toning up the organism, and favoring growth. City air is not good for rachitics; they need the pure air of the country or sea air. We ought, therefore, whenever possible to take rachitic children away from their city surroundings

and put them in the country, and when there they should not be kept in the house but should be out as much as possible in the open air, exposed to the vivifying influences of sunlight. While the bones are soft and are becoming deformed, walking should be prohibited and the children should be carried about in the nurse's arms or in a perambulator.

Sea air has an admitted advantage over that of the interior, and the effects of a prolonged sojourn of rachitic children at the seashore are often most striking. An Englishman, R. Russell, was the first to proclaim the advantages of thalassotherapy (1750), and it was in England that the first maritime station, Margate, was established. Others on the Continent, Berck-sur-mer, Viareggio, etc., were established later. A society called "l'Œuvre des Hôpitaux Marins" was recently founded in France with the object of establishing maritime sanatoria for the treatment of rachitis and scrofula. In Italy there have been added to the marine stations institutes for rachitis (Milan, Turin, etc.) where children receive both treatment for their disease and education. The marine treatment of rachitis is superior to all others and is all-sufficient for mild cases and those of medium severity. After a few months' residence at the seashore the children grow almost out of recognition, the curvatures are straightened, the anæmia disappears, and all the vital functions become reëstablished with energy. That which is the most striking and which enables us to measure the rapid results of thalassotherapy is the enormous growth in weight and in height of the children. The best results of marine treatment are obtained in very young children who make a prolonged stay at the seashore, but we cannot expect to cure the disease by this means when the deformities are of long standing and the bones have become eburnated. The children should be sent to the seashore at the beginning of their trouble, when the disease has not had time to complete its evolution.

A child may profit by thalassotherapy without taking sea baths; salt air and the sojourn on the beach will often suffice; still, baths should be given to all those who can bear them. In default of sea baths salt baths should be given at home, for they have a beneficent action, although an indirect one, on the general nutrition. My custom is to prescribe a bath of twenty minutes' duration, containing one, two, or three kilograms of chloride of sodium, according to the age of the child, every day or every other day. The natural chlorinated sodic waters may advantageously replace these baths at home. Such waters are those of Salies-de-Béarn, Salins du Jura, and Biarritz. A distinguished physician, now dead, Dr. Foix, who practised at Salies-de-Béarn, wrote in 1883: "Rachitis in its early stages is cured

constantly and with extreme rapidity. My custom is to omit all other treatment, while the baths are being employed, but to prescribe an appropriate medical course after their discontinuance. After the third or fourth bath the results are most evident, the curvatures of the bones have already diminished, and, repose aiding, they rapidly disappear. When the malady is more advanced the results are slower but none the less constant; the curvatures of the limbs and the swelling of the epiphyses disappear. The most rebellious deformities are undoubtedly those of the spinal column, which yield nevertheless to the combined employment of douches and of a suitable corset; those of the sternum, which disappear in turn, and especially the flattening and falling-in of the ribs; and finally the deformities of the pelvis."

After the baths it is proper to speak, as stimulants of the skin, of *electricity*, alcoholic lotions, and dry friction. The electrical treatment of rickets has been much vaunted by an Italian physician, Dr. Tedeschi, of Padua (1882); he employed continuous currents and the electric bath. In using continuous currents we apply the electrodes along the spinal column, one pole at the right of the cervical vertebræ, the other at the left of the lumbar vertebræ, the current being passed for two minutes in a downward, and two minutes in an upward direction; this is to be repeated every day. Soon, under the influence of this treatment, we see the sweating, the insomnia, the pains, the glottic spasm, etc., disappear. In thirty-seven cases Tedeschi had but two failures.

Particular attention should be paid to *alimentation*. The food should be as rich and as digestible as possible, such as milk, cream, *purée* of vegetables, eggs, etc. Those articles, which are rich in phosphate of lime (*purée* of lentils and beans, calves' brains, sweetbreads) are to be chosen by preference. The natural phosphates, those which have been assimilated by plants, should be preferred to the phosphates of the shops, which are possibly not absorbed and are always of doubtful utility. Hygiene is of more importance than drugs. However, analeptic remedies, such as cod-liver oil, phosphate of lime, and phosphorus, are very frequently prescribed.

Cod-liver oil was recommended especially by Bretonneau and Trousseau; the yellow oil, containing the alkaloids, is to be preferred to the white oil, from which they have been removed. In general the amount should be rapidly increased until pretty large doses are being given. Carmichael, however, advised the exhibition of small doses, or even frictions with the oil from which very little absorption could be expected. In order that the oil may be tolerated by very young children it should be mixed with some syrup. The animal or vegetable fats, which several have advised as substitutes for the fish

oil—such as butter, lard, tallow, olive oil, etc.—are of no value since they contain no iodine, phosphates, or ptomaïnes to which cod-liver oil owes so much of its efficacy.

The action of this oil is explained by A. Gautier and L. Mourgues as follows: 1. Cod-liver oil acts through its fatty bodies which are readily assimilable, thanks to their partial saponification by the action of the hepatic ferments and by the dissolution of a certain quantity of biliary matters. The fatty bodies are the reserves which are stored in certain of the tissues and are destined to be utilized by the economy to supply the need for calorification. They cannot, therefore, be replaced by less digestible fats or fatty acids. 2. This oil acts as a repairer of the tissue in virtue of its richness in phosphate, phosphoglyceric acid, lecithin, and phosphorus in organic combination. The small amounts of iodine (3 or 4 cgm. per litre) or of bromine also aid in this reparative action. 3. Finally, the oil acts by its alkaloids, which are found in the colored oils and render them more active than the white oils.

J. Bouillot has isolated the alkaloids of cod-liver oil and has administered them in doses of 15 to 25 cgm. in the twenty-four hours. In the case of two children suffering from malnutrition, the appetite returned under this treatment in a few days. Cod-liver oil, the administration of which should be continued for a considerable period, is indicated especially in the case of emaciated and cachectic children tainted with scrofula or tuberculosis.

Phosphate of lime may be given in powder (tricalcic phosphate) or in a slightly sweetened acid solution (solutions and syrups of the phosphate or of the chlorhydro- or lactophosphate of lime). At the present day the glycerophosphates, which seem to be more directly assimilable, are often prescribed in doses of one to four teaspoonfuls a day. Sometimes lime syrups are added to cod-liver oil, making a mixture that is well borne by the little patients. For very young children a suitable form of alimentation is phosphated milk, containing from 5 to 7 gm. of phosphate of lime per litre. This is obtained from cows supplied with fodder grown in a soil highly charged with phosphates.

Pure *phosphorus* has been tried first by Trousseau, who prescribed it in the form of phosphorated butter (1 cgm. phosphorus to 300 gm. butter) spread on thin slices of bread, then by Kassowitz who regards phosphorus as a specific remedy in rachitis. The drug may be given after the following formula:

℞ White phosphorus, ... 0.1 (gr. iss.)
Cod-liver oil, ... 1,000.0 (Oij.)
M. Sig. One to two teaspoonfuls a day.

Oil of sweet almonds may be substituted for cod-liver oil. The mixture may be rendered palatable by syrups or aromatic substances, such as peppermint, anisette, strawberry syrup, etc. The daily dose of phosphorus ought not to exceed 1 or 2 mgm. (gr. $\frac{1}{64}$–$\frac{1}{32}$), or even less. This remedy, according to Kassowitz—whose enthusiasm, however, I do not share—will hasten the closure of the fontanelles, cure the craniotabes, prevent glottic spasms, and bring about a rapid cure. However this may be, phosphorus does no harm when employed in minute dose and may very well be added to an oily menstruum which increases its action.

Other remedies may be employed according to the indications—iron to combat the anæmia, iodine to overcome the obesity, quinine and strychnine as a tonic for cachectic children whose vital functions are sluggishly performed. If there is enlargement of the spleen arsenic should be given in doses of five or ten drops of Fowler's solution per day. When there is scurvy or hemorrhage from any part we should insist upon the use of fresh meat and of the juice of acid fruits, such as oranges, lemons, and grapes.

Surgical Treatment of the Deformities.

When all has been done and especially if the maritime treatment has been tried, and the deformities still persist or are increased, we must have recourse to surgical and orthopedic measures.

Manual Reduction.—The curvatures in rachitic bones can be reduced manually only in the case of very young children. The patient should always be anæsthetized by means of ether or chloroform, and after the limbs are straightened they should be placed in a retentive apparatus (well padded) in order to prevent a return of the deformity.

Mechanical Straightening.—An apparatus devised by V. Robin, of Lyons, enables us to break the bones at any desired point, producing subperiosteal fractures which heal rapidly. This procedure, called osteoclasis, has the advantage of being free from all danger. The bones should not be immediately straightened, but the fractured limb should be placed in a plaster splint in its vicious position and the reduction of the deformity should be delayed for three or four days, at the end of which time the member may be placed in an immovable apparatus in the desired position.

Osteotomy.—When the curvature of the tibia or of the femur is excessive, osteoclasis is not sufficient. We must incise the soft parts and attack the bone at its point of greatest convexity by means of linear or cuneiform osteotomy. The latter consists in the removal of a wedge-shaped piece of bone from the convexity of the curve, in

order to permit of the straightening of the limb. Of course the operation should be done aseptically.

Orthopedic Treatment.—Rachitic children are often made to wear apparatus destined to straighten the bones or to prevent the turning of the ankles. These consist of boots, stiffened with splints, or of retentive apparatus extending up to the thigh or even to the hip. H. Martin, of Lausanne, claims to cure knock-knee by Venel's orthopedic splint. This is made of two bars of steel extending on either side of the leg from the upper third of the thigh to the lower part of the leg; by means of suitable straps and pads the knee is retained in this apparatus while pressure is brought to bear upon the inner surface of the articulation. The apparatus should be reapplied several times a day and each time the joint should be manipulated so as to aid still further the action of the splint. Rachitic scoliosis must be treated by Swedish movements and by plaster or other forms of jackets.

All these measures, which are more or less painful, expensive, and uncertain in their results, are only too often rendered necessary by the carelessness which has permitted the disease to run through all its stages. In order to avoid this necessity of operative or instrumental interference we should combat rachitis energetically by means of the hygienic and medicinal measures just outlined. And we ought especially never to give over to the surgeon a rachitic child until we have tried the effects of thalassotherapy, which is, without any doubt, the most efficacious of all methods of treatment.

Taken in time the disease is curable in the vast majority of cases by purely medical measures; but neglected, unrecognized, or badly treated, it produces deformities which are irremediable without the intervention of the surgeon.

THE DISORDERS OF MENSTRUATION.

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THE DISORDERS OF MENSTRUATION.

Before considering the various disorders to which menstruation is subject, a few words regarding normal menstruation seem appropriate.

Menstruation, without considering its intimate physiology, is characterized by a flow of blood which is periodical and temporary, and which commences in the female at puberty. In our climate it is usually between the ages of twelve and fifteen that menstruation makes its appearance along with all the other symptoms of puberty. The date of the appearance of the menses is governed by general or individual causes, such as the race, climate, latitude, social condition, mode of education, of alimentation, occupation, constitution, hygiene in general, etc. The menses are very exceptionally found to occur from the time of birth, or, what is more frequent, during the first few years of life. This is called *precocious menstruation*. This precocity appears to have no influence on the ulterior evolution of the function of menstruation; nevertheless a certain coincidence between this abnormality and cancer on the one hand, or a later menopause on the other, has been remarked by certain observers.

The Menopause.—This occurs at the age of from forty-six to fifty, which implies that the genital life of a woman of our climate has a duration of from thirty to thirty-six years. But here, also, exceptions are not rare, and especially cases of long continuance. Symptomatic metrorrhagia depending on uterine, ovarian, or tubal affections, which occurs after the usual age of the menopause, is often mistaken for the menses, though there are some unmistakable cases recorded of true menstruation which lasted as late as the fifty-fifth, sixtieth, and even seventieth year. In practice, these late flows, in spite of their apparent periodicity, should always be regarded with suspicion as denoting some serious lesion seated either in the cervix or in the corpus uteri. A. R. Simpson states that not infrequently the climacteric is preceded by two or three periods of excessive flow of blood without there being any pathological change in the uterus.

On the other hand, precocious menopause has been met with occurring at the age of forty, thirty, or even twenty-seven.

What is the physiological mechanism of menstruation? It is not

our intention, in this short résumé of the subject, to discuss the theories which have been emitted upon this question. We will, however, say that supporters of the classical theory of ovulation (Megnier, Coste, Bischoff, etc.) have been completely overthrown by Beigel, de Sinéty, Lawson Tait, and others. We may admit for the time being that ovulation and the menstrual flux are two phenomena usually connected with one another, but not necessarily united to each other. For that matter, none of the more recent theories can successfully overthrow the old one.

Recently Byron Robinson has emitted a theory which should be mentioned here, inasmuch as it explains at the same time the flow of the menses as well as their periodical appearance. According to this writer, there is in the walls of the tubes and uterus a certain number of small ganglia which he calls the automatic ganglia of menstruation and which are analogous in their functions to the ganglia of Bidder, Schmidt, Ludwig, Remak, and to the plexus of Auerbach and Meissner, which preside over the rhythmic and periodical function as well as over the uterus and the tubes. His assertion is based on experiments in comparative physiology and on anatomical researches. The ganglia in question may sometimes be seen with a strong magnifying glass; the sympathetic nerves which go forth from them enter into the tubes and the corpus uteri, while the branches coming from the sacral plexus innervate the cervix.

It is the mucosa of the corpus uteri that undergoes the greatest changes in its structure during menstruation. Leopold gives the following résumé of these changes: Hypertrophy and congestive œdema of the endometrium; modifications of the glands, which are elongated, hypertrophied, and irregular in shape; dilatation of the lymphatic spaces; infiltration of the stroma with embryonic elements, while on the surface giant cells are to be found. The exit of the red blood corpuscles occurs by diapedesis and by rupture of the superficial vascular networks.

It was believed that at each menstrual period desquamation of the mucosa occurred, but the researches of Kundrat, Leopold, Maricke, de Sinéty, and others, have demonstrated that it remains intact. There is probably an exaggerated secretion from the uterus and tubes, but no degenerative changes. The mucous membrane of the tubes undergoes changes identical to those of the endometrium; that of the cervix only secretes more abundantly.

The quantity of blood which flows away at each menstruation varies with each woman, and may differ in the same subject from one month to another. The mean quantity lost at each menstruation is from 100 to 300 c.c. At the beginning and at the end of each period

the blood is mixed with mucus and presents a lighter color. During the height of the process it has the characteristics of venous blood. It is rich in carbonic acid and contains mucus; there is little tendency to coagulation. Nevertheless, if it transudes abundantly and remains in the uterine cavity, it may form clots there, and these when expelled will produce pain, which is known by the name of uterine colic. The odor of the menstrual blood, which is *sui generis*, is due to the changes that it undergoes on account of the slowness of its exit and its admixture with the vaginal secretions. This odor is for that matter less pronounced the more the woman is attentive to her toilet.

The older writers attributed virulent properties to menstrual blood, but good sense and observation have long since demonstrated the folly of this idea. Nevertheless, Barnes admits that in certain cases, in which there is retention, a kind of *menstrual toxæmia* may occur which is due to the resorption of the altered blood and is analogous to certain forms of autogenetic puerperal fever. It is also probably true that in many women who have latent gonorrhœa lingering in the mucosa of the cervix uteri, the gonococci are brought down into the vagina at and just after the menstrual period, so that coitus at this time only may give rise to infection.

All parts of the genital system, ovaries, broad ligaments, vagina, vulva, and breasts, participate in the menstrual congestion.

At the time of the first menstruation, the organism of the female undergoes profound modifications, all of which constitute puberty. The pelvis becomes larger, the growth of hair on the pubis becomes marked, the breasts and the thyroid gland develop, etc.

The appearance of the blood may occur without any prodromes in young girls who are healthy, and may often take place without any warning. But usually, especially in women living in large cities, the first menses are preceded by a lassitude, a feeling of fulness in the pelvis and in the lumbar region, headache, flashes of heat, vertigo, changes in the individual character, frequent desire to pass water, pruritus of the vulva, painful swelling of the breasts, and a number of other phenomena. All these symptoms usually diminish as soon as the flow is established, but sometimes they persist during the entire time of the flow.

When once established, the menses appear every twenty-eight or thirty days during the entire genital life of the woman, with the same general and local signs more or less marked. All these taken together constitute what is called the menstrual molimen.

It is not infrequent to witness at the time of the menses, although they may be perfectly normal, a certain number of periodical cutaneous manifestations, such as eruptions of herpes, of acne, urticaria,

pemphigus, eczema, erysipelas, etc. Recently, one or two works have appeared describing a so-called angina of menstruation which is a form of subacute tonsillitis. Other congestive processes have also been mentioned such as parotiditis and an exaggerated swelling of the thyroid gland.

During this period women should avoid sudden changes in their manner of living, any great emotion or mental impression, be it either local or general; cold should be avoided as well as coitus. All causes, even slight, of infection should be carefully prevented, because the endometrium is at this time in a condition which is particularly favorable for the retention and culture of the infectious bacteria. There is no doubt in our minds but that very many cases of endometritis, which so often occurs in the virgin or the multipara, are due to improper care, both local and general, during the menstrual periods.

Amenorrhœa.

Amenorrhœa, in the strict sense of the word, is the complete absence of periodic, sanguineous transudation from the utero-tubal mucous membrane. This definition excludes those cases in which retention of the menstrual blood is due to any mechanical obstruction, such as imperforate hymen, congenital stenosis of the cervical canal, etc.

Amenorrhœa is physiological before puberty and after the menopause, as well as during pregnancy and lactation.

The intermittent hemorrhages that are occasionally observed at the beginning of or during pregnancy are caused by a congestive transudation or are due to an organic lesion of the cervix or body of the uterus, as well as to threatened abortion. These flows have never rigorously the characters of periodicity, duration, quantity, and quality of true menstruation. The menses reappear generally at about the forty-fifth day after labor, if the woman does not bring up her child at the breast.

During lactation there are very frequent exceptions to the rule of normal amenorrhœa. It is not infrequent to see very good nurses who have their catamenia after the sixth or the eighth month, or even at the usual time at which the menses would return after labor, were the child not breast-fed. In these conditions the milk is simply less rich in fatty matter, and the chances of fecundation are very largely increased.

Etiology and Pathology.

The causes of pathological amenorrhœa are to be found either in the genital organs, in the general condition of the patient, or in the nervous system.

The Genital Causes.—Permanent and spontaneous amenorrhœa is usually produced by an arrest in the development of either the entire genital system or a part of it.

Amenorrhœa may be only apparent in cases in which there is congenital or acquired atresia of the genital canal resulting in hæmatocolpos and hæmatometra, diseases which cannot be considered here, as they belong under the head of genital malformations.

As we have said, real amenorrhœa depends on a pathological condition of the uterus, the tubes, or the ovaries. Diseases to which the ovaries are subject do not produce amenorrhœa unless these organs are in a very degenerated condition. We have seen cases of microcystic degeneration of both ovaries in the same individual, in which the organs were riddled with cysts, a small portion of healthy ovarian tissue only remaining; and still these patients had menorrhagia. The presence of even large tumors of both ovaries does not cause amenorrhœa. Surgical suppression of the totality of both ovaries produces artificial amenorrhœa immediately, or if not immediately, very shortly after. We think that this is the opinion which is generally admitted to-day. The cases, which for that matter are quite numerous, in which there is a temporary or permanent continuance of menstruation after bilateral ablation of the ovaries can be explained by the presence of a supernumerary ovary or of a piece of ovarian tissue which had escaped the knife, or by the persistence of uterine lesions, or, lastly, by a kind of organic habit. All other reasons are open to great suspicion, except the one that some portion of ovarian tissue has been left behind, either by inattention of the operator or because some part of an ovary was in the broad ligament separate from the rest of the organ.

Tubal amenorrhœa is very infrequent, because diseases of the tubes, even such as suppurating salpingitis in which the canal of the tube is transformed into a purulent cyst, do not prevent menstruation if the ovary and the uterus remain healthy. This, however, is rarely the case, as the endometrium in cases of salpingitis is usually in a state of more or less pronounced inflammation. As to the functional or surgical suppression of the tubes, it is absolutely impossible to draw any conclusions from the cases which have been reported,

because the results as regards menstruation are so diametrically opposed to each other.

The diseases of the pelvis in general rarely cause amenorrhœa.

Uterine amenorrhœa, that which has some affection of the uterus for cause, is relatively rare. It may accompany inflammation, displacements, or tumors of this organ, although these affections usually produce metrorrhagia; but in atrophy of the uterus, be it either congenital or acquired, after labor, inflammation, or violent cauterization, amenorrhœa will be the prominent symptom.

General Causes.—All acute and chronic diseases which may delay the development of the genital organs, modify the composition of the blood, or profoundly deplete the organism, may produce amenorrhœa. Thus chlorosis, scrofula, anæmia, tuberculosis, either at the beginning or in the later period; typhoid fever, albuminuria, diabetes, the various cachexias, either medical or surgical; intoxications from alcohol, morphine, or syphilis—all these act in different degrees. Menstruation, like digestion, like the greater part of the functions of the economy, is produced only in a healthy organism; disease arrests it or hinders it. Besides the diseases already mentioned pertaining to the etiology of amenorrhœa, obesity must certainly not be forgotten. It is also necessary to take into account the hygienic condition of the patient, because a want of air, light, or exercise, too much physical or intellectual work, insufficient nourishment, or a sudden change of alimentation are certainly prominent factors in the etiology of this menstrual disorder.

Nervous Causes.—These act by inhibition, or by a vasomotor perturbation, and, generally speaking, cause only a transitory arrest of the menstrual flow. A great moral emotion, no matter to what it may be due, a sudden cooling down either of the entire body or simply of the genital organs, surgical shock, etc., are occasionally the cause of a sudden arrest of an already commenced menstruation, and may ultimately produce amenorrhœa.

Hysteria, epilepsy, certain forms of mental disease, and myelitis have amenorrhœa as one of their symptoms; and lastly, it may have as a cause direct suggestion, or a kind of autosuggestion by fear of pregnancy, or by an extreme desire to be pregnant. These cases of amenorrhœa by autosuggestion are far from infrequent. Several cases have come under our observation in Europe which were cured by hypnotism. Generally speaking, this form of amenorrhœa does not persist for any length of time.

There are cases of amenorrhœa in which the most attentive and careful examination can show no pathological condition of the female organs of generation. These cases we should diagnose under the

name of idiopathic amenorrhœa. This is a classification, however, that will little by little disappear as the science and art of gynecology progress.

Symptoms.

Amenorrhœa, unless it is congenital, comes about, according to the cause, more often insensibly than by sudden arrest of the function, although under certain conditions it may be sudden and occur in the midst of the menstruation.

Whether the trouble be permanent or transitory, the menstrual period may go by unnoticed or may be recalled simply by the menstrual molimen, or may give rise to various troubles, such as cutaneous exanthemata, which we have already mentioned, or to exaggerated disturbance of the nervous system, which may go so far as to produce convulsions, sensorial perturbation, and even paraplegia.

The flow of blood is occasionally superseded by supplementary secretions, such as leucorrhœa, diarrhœa, or hyperidrosis, and, lastly, it may occur periodically from other parts of the body, a condition of affairs known as vicarious menstruation. The mucous membrane of the nose, the bronchial tubes, the stomach, and the rectum, are the most frequent seats of this abnormal condition. Exceptionally, the flow of blood has been observed to come from the ear, from the surface of a tumor, or from a cutaneous wound. Although many of the cases of this sort are subject to a certain amount of doubt, too many trustworthy instances have been recorded to permit of scepticism, so that the fact must be admitted to-day.

Prognosis.

Amenorrhœa is often only a simple delay of the appearance of the menses, which may last a few years; and in this case it is due to an arrest or a delay in the development of the organism. Menstruation will establish itself with regularity later on.

When amenorrhœa is permanent, it is not incompatible with a health which otherwise is perfect; neither does it exclude the possibility of fecundity or pregnancy, and cases of permanent amenorrhœa are on record in which the subjects were mothers of healthy children. Likewise cases have been recorded in which patients who have had amenorrhœa up to the time of their first or second pregnancy, have eventually menstruated after bringing their children into the world.

The prognosis of occasional amenorrhœa varies according to the lesion which produces it. It is often a phenomenon which is not to be considered; often it is the indication of serious lesions of some organ or organs of the economy. When amenorrhœa has an

emotion or nervous shock as its etiological factor, it is sometimes of short duration, and may cease under the influence of a cause similar to that which produced it.

Diagnosis.

Amenorrhœa can only be mistaken for a mechanical retention of the menses by imperforation or obstruction of the genital canal; but these causes, which might lead the practitioner into error, are easily detected if direct examination of the parts be made, and this should never be neglected under any consideration.

In a young woman or a young girl who formerly was regular, and in other ways of good health, suppression of the menses should lead the physician to consider the question of a commencing pregnancy, and the signs of this condition should be carefully sought for; but as they are known to all, we will not give them here. If the menstruation has previously been irregular, and the patient is in the grasp of some chronic affection, the diagnosis may be much more difficult to arrive at, and oftentimes it is better to wait and watch the patient before either making or rejecting the diagnosis of pregnancy. It should never be forgotten that there is a so-called *nervous pregnancy*, caused by an excessive desire to have children, or, on the contrary, great fear of conceiving. But these cases are infrequent, and if the patient's history is carefully examined into, there should be, we think, no difficulty in coming to a correct conclusion.

If the amenorrhœa is really pathological, the cause is the first point to determine. The solution of the problem is generally easy; most often the physician finds himself in the presence of a young woman, pale, slight, lymphatic or nervous, and presenting the stigmata of scrofula, or the signs of an overworked system, either mental or physical. A physical examination of these subjects should be made with the greatest precision and detail, none of the systems being neglected, because in the majority of cases some latent disease, particularly pulmonary tuberculosis or heart disease, will probably be discovered. The menstrual disorder in these cases is either due to an incomplete development of the genital apparatus, which will be found out only by direct examination under ether or chloroform, or the general condition of the subject may sufficiently explain the abnormality; or, on the other hand, both these causes may be combined in one patient.

When amenorrhœa is accompanied by pelvic symptoms, it is associated with a peri-uterine or uterine lesion, which will be discovered by a properly conducted examination and by a proper questioning of the patient. As to vicarious menstruation, in order to be char-

acteristic it should be periodical and coincide with the menstrual molimen and absence of flow of blood from the genital tract.

Treatment.

The care of patients presenting amenorrhœa should be considered especially as regards the cause. If the amenorrhœa is symptomatic of a uterine or peri-uterine disease, the latter should first be treated. In the case of microcystic degeneration of the ovaries, the daily application of a twenty-five-per-cent. solution of thiol in glycerin on large wool tampons is indicated. Ichthyol or thiol tampons are also of great value in the various inflammatory uterine disorders. The hot douche is also frequently employed, and with good reason, in these cases.

If the subject be a young, chlorotic woman, living under bad hygienic conditions and presenting tardy development or inactivity of the utero-ovarian system, the physician should order a good, nourishing diet, walks in the open air, gymnastics, hydrotherapy; massage of the abdominal organs, or alcoholic frictions over the abdomen; tonics such as iron, chalybeate waters such as those of St. Leger or Orezza; or arsenic, inhalations of oxygen, static or faradic electricity; the emmenagogues, such as saffron, ruta graveolens, oxalate of cerium, apiol, oxalic acid, permanganate of potassium, salicylate of sodium, should be administered only with great precaution. The permanganate of potassium, given in a dose of from 5 to 10 cgm. daily, has been praised of late years as a remedy for amenorrhœa in young girls. The peroxide of manganese in the dose of 10 cgm. thrice daily is also of value. Iodide of potassium in increasing doses, beginning with 50 cgm. daily, increased to 3 gm. in twenty-four hours, is also very highly recommended, although it has not proved particularly successful in our hands. Primary amenorrhœa is well treated by the administration of four drops of tincture of pulsatilla thrice daily. The tincture of pulsatilla given in conjunction with tincture of caulophyllum is also of considerable value and may be prescribed as follows:

℞ Tinct. pulsatillæ, ... 5.0
Tinct. caulophylli, ... 10.0
M. S. Take fifteen drops in water three times daily.

Oxalic acid is also much in vogue as an emmenagogue. The following formula is given as an example of its mode of administration:

℞ Acidi oxalici, ... 0.50
Syr. limonis.
Aquæ, ... āā 50.0
M. S. A teaspoonful three times daily.

The action of this drug is not, however, without some amount of danger as has been pointed out by Talley, and for this reason the physician should carefully watch the patient during its exhibition. It appears to have a direct stimulating action on the uterine mucosa, and is consequently indicated in the amenorrhœa of anæmic or plethoric women.

In married women the intra-uterine faradic current, or, better still, the galvanic current is certainly of considerable service.

In plethoric or obese women, proper regimen with emmenagogues, electricity, counter-irritation over the spinal column and on the inner aspect of the thighs at the supposed time of the menses, are useful in the treatment of this disorder. Foot baths or hot sitz baths produce congestion of the pelvic organs and thus may establish the flow. Scarification of the cervix is also recommended.

The repeated passage of the uterine sound, dilatation, curettage, intra-uterine applications of tincture of iodine or of a solution of creosote in glycerin, 1:5, may also be tried, as well as painting the abdomen and cervix with tincture of iodine.

In cases of tuberculosis or other wasting diseases, the treatment of amenorrhœa naturally is that of the disease causing the arrest of the menses. Emmenagogues, drastics, counter-irritation on the lower limbs, are often successful in the relief of amenorrhœa from cold or from emotion; this form may cease spontaneously under the influence of a new emotion, in which case the latter acts like a counter-irritant. In acute arrest of the menses, accompanied as it often is by an elevation of the temperature, the tincture of aconite given in the dose of one drop every hour will be found of service.

Marital intercourse is often sufficient to bring about the development of the genital organs, as well as to regulate their functions; and lastly, there are certainly a number of cases in which the nervous element predominates, in which suggestion seems to be a highly efficacious method of treatment.

The physician should always endeavor to bring back the menstrual flux to the natural passages by the means which we have enumerated, when the discharge of blood takes place from some other mucous membrane or from the skin. The amenorrhœa depending on stenosis of the cervix must be treated surgically; forced dilatation or incision with a blunt-pointed bistoury or metrotome may be practised.

Menorrhagia.

Menorrhagia is an excess in duration and in quantity of the menstrual flux; metrorrhagia differs from it only in that it occurs at

irregular intervals. Now, as a matter of fact, the normal menstruation varies in duration from two to nine days; consequently, when we think of such an enormous difference in the duration of the flow in the normal state, it is necessary, in order to appreciate a trouble of the menstruation, to take a special clinical average rather than follow a rigorous and general definition.

Etiology and Pathogenesis.

In the true sense of the word, there is no essential menorrhagia, the condition being always the result of general or local causes.

General Causes.—All dyscrasic affections, such as scorbutus, purpura, the various intoxications, Bright's disease, Werlhof's disease, etc.; diseases which produce disturbances in the circulation, such as affections of the heart itself, of the liver, or of the kidneys, and various tumors.

Scrofula predisposes the mucosa in general, and the endometrium in particular, to hyperplasia and transudations of blood.

Some of the pyrexias, especially the exanthemata, occurring at about the time of the menses, increase the duration of the flow and the amount of blood lost. The metrostaxis, called by Gubler uterine epistaxis, which is so often met with in typhoid fever, may be given as an example.

Plethora, obesity, chlorosis, anæmia, tuberculosis, and many other troubles produce, according to the case, menorrhagia which may alternate with amenorrhœa.

Menorrhagia has also been observed to occur from lactation, fatigue, emotions, or, outside of all local affections, on the arrival of puberty or at the first sexual connection.

Local Causes.—The uterine or peri-uterine diseases taken altogether have menorrhagia or metrorrhagia as a nearly constant symptom. Whether it be the reflex action from venous stasis, or a pathological condition of the endometrium, we think that it is safe to say that about two-thirds of the cases suffering from menorrhagia or metrorrhagia are due to a diseased condition of the uterine mucosa.

Besides the lesions of the endometrium, there may be metrorrhagia from the diseases of the tubes and ovaries. The three organs, uterus, ovaries, and tubes, should be taken as a group, because when blood flows from the uterus it is in many cases difficult to know exactly what may be the source.

Ulcerations of the cervix bleed easily when touched with the finger, or by the male organ during coitus. The hemorrhage is spontaneous when there is an epithelioma; but in these cases it is slow, prolonged, and not very abundant, and the fluid is thin.

In passing, we would remark that the vulva or vagina may present some pathological condition which may give rise to hemorrhage, such as tuberculous or cancerous ulceration, or the rupture of a varicose vein.

The four principal causes of menorrhagia or metrorrhagia, which are to be found in the corpus uteri, are metritis, fibroma, cancer, and sarcoma. Cancer and sarcoma of the corpus are rare as primary affections; when secondary, they occasion watery hemorrhages, small in quantity. Fibroids situated in the walls of the uterus and which tend to progress toward the interior of the uterine cavity, are the cause of abundant and prolonged hemorrhages.

In hemorrhagic metritis the inflammation of the mucosa is interstitial or mixed, both glandular and interstitial, but with the predominance of lesions in the stroma. The purely interstitial form is found in the aged, while in young women the lesions of the stroma predominate, and the glands do not completely disappear. There is a great vascular proliferation in the hemorrhagic form. The newly formed vessels, which are only capillary, are irregular and of relatively large calibre. They are seated very superficially at the surface of the endometrium, while the greater part of the cul-de-sac is situated below them. The hemorrhages are thus accounted for by the considerable number of vessels so superficially seated, and consequently the characteristic lesions of the hemorrhagic metritis are the marked changes in the stroma. We will also add that this disease is not due to infection, but may have for its starting-point a small particle of retained membrane, and from this centre the endometrium becomes involved.

Simple hypertrophic metritis may also give rise to hemorrhage, especially when the so-called mucous polyps are present.

The diseases of the tubes, either in themselves or by the congestion that they cause in the uterus, may bring about hemorrhages from the genital tact. The part they play in this instance, however, is as yet only imperfectly known.

The influence of the ovaries is more definite and precise. Their activity is probably, at least in part, the source of the menstrual hemorrhage, while their excessive activity increases the flow of blood and produces a pathological condition. The source of the blood is in general the endometrium itself, as we have already seen, but the ovary acts upon the latter by reflex action. Consequently, when a woman is subject to metrorrhagia, the cause of which we cannot determine, and the flow of blood is difficult to control by the various therapeutical sources, especially curettage, the physician should never neglect a careful examination of the

ovaries. Inflammation, prolapsus, compression, or degeneration of these organs is often the cause of the hemorrhage, and in serious cases the removal of one or both glands is sometimes the only remedy which will really control the loss of blood. Pozzi certainly deserves the credit of having performed partial resection and ignipuncture of the ovaries in cases of microcystic degeneration; and in many of his cases, numbering in all some eighty or ninety, in which he has performed this operation, leaving perhaps only a bit of normal ovarian tissue, pregnancy has been the result. In removal of the ovaries, if this operation should be resorted to, especially when they are prolapsed and easily reached with the exploring finger in the vagina, anterior or posterior colpotomy is often an excellent method to adopt for reaching the diseased organs. At the time of the beginning of menstruation, but especially at the menopause, hemorrhages are often seen to occur. These metrorrhagias, which are infrequent and of only slight gravity when they occur at puberty, are frequent, serious, and very obstinate where they occur at the menopause. In fact, they resist about all the methods of treatment that have been devised for their cure. In all such cases there should be the gravest suspicion of malignant degeneration of the uterus, and local examination, with curettage and microscopical diagnosis, is imperatively indicated.

Metrorrhagia may also occur during pregnancy, and then it is often due to some lesion of the uterus which we have mentioned above; but more frequently the flux is due either to the return of the menses—in which case it is in about the same quantity as normal menstruation—or to the detachment of a normally implanted placenta or of a placenta prævia. In this case miscarriage is always to be feared. When a hemorrhage occurs after an amenorrhœa of some months' duration, the possibility of pregnancy should be considered, and if this is the case, the physician is, in all probability, in the presence of a threatened miscarriage. The diagnosis is ordinarily very easy in the second half of pregnancy, but in the first four months it is often very difficult to come to a decision.

Among the pathological conditions of pregnancy which are susceptible of producing hemorrhage, extra-uterine pregnancy, placenta prævia, and hydatidiform mole are to be particularly mentioned. These hemorrhages, as well as those occurring during labor or post partum, are in the domain of obstetrics, and we will not treat of them here.

Symptoms.

The symptoms of menorrhagia are as follows: The blood, which is more abundantly excreted, coagulates more easily and the expulsion

of the clots provokes colic. The duration and the quantity of the flux are extremely variable in different subjects, and in the same subject at different times. It may even form in itself a real pathological condition, ultimately resulting in anæmia with all its consequences, all the more so when it is associated with metrorrhagic symptoms. On the contrary, it acts like a favorable bleeding when it occurs in plethoric females or those suffering from a cardiac lesion.

There is no pathological anatomy proper to menorrhagia. In each particular case, the existing lesions of the affection which is the cause of the hemorrhage are alone to be considered; but, as we have said, in a large proportion of cases some form of endometritis exists.

Prognosis.

The prognosis depends on the affection which is the cause of the menorrhagia. However, it must not be forgotten that menorrhagia aggravates some of the diseases which give rise to it, such as chlorosis, and anæmia; and still more, it diminishes the aptitude of fecundation, and is certainly a prominent cause of miscarriage.

Diagnosis.

There is really menorrhagia only when the flow of blood acts in a bad way on the health of the patient, and when it occurs periodically. When menorrhagia is associated with metrorrhagia, the patients often are no longer able to keep run of the date on which their menstruation proper should occur, as is often the case in hemorrhagic metritis.

The diagnosis, as a matter of course, should be, before all, etiological. It is the uterus which should first be examined, and as we have said, in the great majority of cases this organ, or the adnexa, will be found in a pathological condition which will sufficiently explain the menorrhagia. If the local examination shows no lesions, the general condition should be looked into, and all the viscera should be carefully explored in order to ascertain the disease which is probably present.

Treatment.

The immediate treatment of menorrhagia or metrorrhagia has for its object to combat the immediate or near danger of an excessive loss of blood. In order to obtain this, absolute rest in bed is indicated, the patient lying on the back with the head low, and the foot of the bed raised; cold vaginal irrigation, which must always be a continued flow, or what is perhaps better, a hot-water irrigation at the temperature of from 40° to 48° C., prolonged and repeated, with

the addition of perchloride of iron, if necessary, should be ordered. The application to the abdomen of a bladder filled with chopped ice is also effective. Ergot, or one of its derivatives, given by the mouth or by subcutaneous injection, acts well. The following formula is an example of a good prescription to be given in metrorrhagia:

℞ Ergotini,
Quininæ sulph., ... āā 4.0
Ext. hyoscyami,
Pulv. digital. fol., ... āā 0.40
M. f. pil No. xl. S. Take from five to ten pills daily.

An infusion of digitalis, 10 cgm. to 1 litre of water, to be taken in twenty-four hours, is also, according to Gallard, an excellent means of arresting the flux. Among other drugs which are in vogue may be mentioned the fluid extract of hydrastis canadensis, antipyrin, and perchloride of iron.

If dysmenorrhœa accompanies the menorrhagia, the hydrastis combined with viburnum will be found a valuable combination, the following formula being given as an example:

℞ Ext. fluid. hydrastis canad.,
Ext. fluid. viburn. prunifol., ... āā 15.0
M. S. Ten drops every two hours in a little sugar and water.

If these means are insufficient to arrest the flow, an antiseptic and methodical tamponnade of the vagina should be practised.

The technique of the tamponnade is as follows: A band of iodoform or europhen gauze prepared for the special purpose should be selected; but simple cheesecloth which has been rendered aseptic by boiling in a one-per-cent. solution of bicarbonate of sodium may be used if the iodoform gauze is not at hand. The patient is placed on the edge of the bed with the thighs drawn well on to the abdomen, and a bivalve speculum is introduced. If it is necessary to perform an intra-uterine tamponnade as well, the cervix should be seized with a stout pair of bullet forceps, which are given to an assistant to hold. The end of the strip of gauze is taken in the grasp of a long slender forceps made for the purpose of intra-uterine dressings, and the gauze is thus carried up to the fundus in the uterus. The instrument is then unlocked and withdrawn, and more of the gauze is seized below and pushed into the cavity. This manœuvre is repeated until the interior of the uterus is solidly packed. After the intra-uterine packing, the vagina should be well filled with packing in its turn.

The technique of vaginal tamponnade is the same as for the intra-uterine. The vagina should be filled from within outward, beginning in the culs-de-sac, and enough gauze should be inserted to

tightly fill it, including all the corners and folds. In order to accomplish this, three or four yards of gauze will be necessary.

The gauze should be left in place from twenty-four to thirty-six hours if it was thoroughly aseptic when it was introduced. While it is in place, the function of the bladder should be carefully watched, because, frequently, retention of urine is caused by the pressure of the vaginal packing on the bladder; in such case the urine should be drawn with a glass catheter every six hours. The physician may often be surprised, when about to introduce the gauze, to find that he is dealing with a pedunculated polypus which has already made its way through the os; but he may find that there is a carcinomatous degeneration of the cervix which is the cause of the hemorrhage. If he is in the presence of a polypus, it is natural, in order to check the hemorrhage, that he should proceed at once with the removal of the growth, in the manner described below.

If it be a carcinomatous degeneration of the cervix in the beginning, the physician should lose no time in performing vaginal hysterectomy, a description of the technique of which would be out of place in this article. The malignant neoplasm is inoperable, if it has already invaded the vaginal culs-de-sac, or if by a careful bimanual palpation the broad ligaments are found thickened and hard to the touch. These two signs are valuable as contra-indications to a radical operation for the removal of the diseased uterus, because when the broad ligaments are found thickened in connection with a cancer of the cervix, this would imply that other lymphatics are already invaded, and consequently hysterectomy would prove of no value.

The palliative treatment for a hemorrhage occurring in cancer of the uterus is, first, a thorough and careful removal with the sharp spoon, followed by thermo-cauterization, of the growth from the cervix and also from the vagina, if it has invaded the latter. A very excellent preparation which we have seen employed, and which we have employed ourselves with the greatest success as a local application for uterine cancer, is equal parts of terebene and olive oil. This should be applied to the parts on a tampon soaked in it, the tampons being changed daily. The effect of the treatment on the growth is really remarkable. The odor and the hemorrhage disappear in a most wonderful manner, and in some cases we have seen healthy granulations spring up where the growth had formerly existed. Unfortunately, like all other remedies for cancer, it is only palliative, yet we wish most highly to commend it in this terrible disease.

In cases of adenoma or carcinoma of the body of the uterus, the use of the curette followed by packing with iodoform gauze will con-

trol the hemorrhage and give an opportunity for microscopic diagnosis if necessary. Hysterectomy should be performed as soon as practicable.

In cases of submucous fibroids, which are the frequent cause of menorrhagia or metrorrhagia on account of their action on the endometrium, which is the source of the flow of blood, the uterus should be dilated either with Hegar graduated sounds or with steel dilators. When dilatation is sufficient for the introduction of the index finger, the uterine cavity may be explored, never forgetting complete asepsis, and the growth may be removed by Vulliet's method—by making an incision in the long axis of the tumor down to its capsule, tamponning the uterine cavity, and changing the dressings daily. Administering ergotin internally will produce expulsive efforts on the part of the uterus, and in the majority of cases the fibroid will be eliminated through the cervix in a comparatively short time. If this operation is resorted to, it must only be under the most rigorous asepsis, because if the uterine cavity becomes infected the growth will become so too. It will then become gangrenous, and septicæmic intoxication will carry off the patient. In this country most surgeons would prefer to perform hysterectomy rather than to take the chances involved in the conservative but rather uncertain method, just described, for eliminating a submucous fibroid, although in certain cases where conditions are favorable the latter is of unquestioned value.

In very serious menorrhagia which cannot be controlled by any of the above methods, no matter what may be its cause, it is proper to ligate the uterine arteries, reaching them by incisions on each side of the cervix; or if time presses, by a needle passed through the mucous membrane in such a manner as to include the artery.

It is only exceptionally, and after failure with all the means that we have indicated above, that we think vaginal hysterectomy, or castration, should be performed, unless the former be indicated for the removal of a carcinoma.

There is, however, one disease which has menorrhagia as a prominent symptom, in which vaginal hysterectomy should be performed with the shortest possible delay in order to save the patient, and that is, the so-called hemorrhagic metritis of old women. This form of metritis is really an adenomatous change of the endometrium, and if the uterus be not entirely removed death is sure to result from subsequent carcinomatous degeneration.

Dysmenorrhœa.

The word dysmenorrhœa signifies painful menstruation, and may be applied in a general manner to those cases in which the ordinary discomforts of menstruation take on a pathological intensity.

Etiology and Pathogenesis.

Our knowledge regarding the physiology of normal menstruation allows us to make only various hypotheses regarding the intimate mechanism of certain types of dysmenorrhœa; such is the case with those which have their origin outside of the uterus, either from lesions of the adnexa or from general diseases. Others, on the contrary, are easily explained by a diseased condition of the uterus; consequently the older divisions, which are certainly more or less confusing, may be simplified without taking into consideration the pathogenic mechanism, and three clinical varieties of dysmenorrhœa may be admitted, namely: 1. Dysmenorrhœa from diseased adnexa; 2. Uterine dysmenorrhœa; 3. Dysmenorrhœa from general disease. These three varieties are very often associated.

We will first speak of the dysmenorrhœa from lesions of the ovaries. Delay in the development of the ovaries or an inequality between the evolution of the uterus and the adnexa; all diseases of the ovaries and tubes; other inflammation, be it either recent or old, of the pelvic peritoneum, such as periovaritis or perisalpingitis, through the secondary influence that it exercises on these organs; pelvic varicocele; neoplasms and tumefactions in the neighborhood of the uterus—all these causes, by the disturbances that they give rise to in regular ovulation either directly or secondarily, produce an exaggeration of the sensitiveness of the ovary or of the uterus, and consequently result in the production of dysmenorrhœa.

Diseases of the tubes, though forming a less important etiological element of dysmenorrhœa, are liable to produce it. Catarrhal or parenchymatous salpingitis plays a certain part in the production of menstrual pain, either by the irritation that it produces in the uterine or reflex action, or by the painful contractions of which the tubes may be the seat, and which is known as salpingitic colic, long since recognized as the *colica scortorum*.

Besides the ovary and the tube, a disease of the perimetrium, such as a phlegmon, a neoplasm, a hemorrhagic or purulent focus, which compresses and displaces the genital organs, may be a potent cause of dysmenorrhœa.

Uterine dysmenorrhœa is usually what may be termed obstructive or mechanical dysmenorrhœa. It is dependent on a temporary or intermittent obstacle to the flow of blood, the spasm of the internal orifice (spasmodic dysmenorrhœa of Matthews Duncan); congenital or acquired stenosis due to an excess in cauterization of the cervix or to tumors such as fibroids or intra-uterine polypi, especially when seated in the neighborhood of the internal os; the displacements, especially flexion and more particularly anteflexion, found associated with an incomplete development of the organ, as well as with stenosis of the cervix and hyperæsthesia of the mucosa—all these are potent factors in the production of dysmenorrhœa.

Uterine dysmenorrhœa may also be due to the various forms of metritis with either hypertrophy of the endometrium and superabundant exudation of blood, or loss of elasticity of the uterine tissues and the compression of the nerve endings which are the result of sclerotic atrophy of the uterus.

All the above-mentioned causes act by diminishing the calibre of the uterine and cervical cavities, or by producing a certain afflux of blood the quantity of which is very much larger than can possibly pass through the utero-cervical canal, which is not wholly normal. Both these mechanisms often go hand-in-hand in the same way as often do the lesions on which they depend.

Regarding dysmenorrhœa from a general cause, all that is necessary for us to say is that any general disease which is capable of producing amenorrhœa may give place to dysmenorrhœa by various similar mechanisms.

There is one variety of dysmenorrhœa which should particularly call for our attention in this chapter, and that is membranous, or, better, pseudo-membranous, dysmenorrhœa. This is characterized by the throwing-off of a membrane from the uterine cavity. Many writers have endeavored to give to this form of dysmenorrhœa an individuality of its own, because the pains of menstruation are accompanied by the expulsion of false membranes. But these false membranes are only one of the symptoms of dysmenorrhœa; consequently there is no sufficient reason for classing this pseudo-membranous form apart from the other kinds of dysmenorrhœa, which should be a unity, and the various forms which have been mentioned above, such as ovarian and uterine dysmenorrhœa, are simply etiological or symptomatic details, which in practice are really of no value. This subject will be considered later more in detail.

The pain of dysmenorrhœa is very similar to miniature labor pains; this is easily explained because in both cases the pains are produced by uterine contractions. During a number of hours preced-

ing the appearance of blood, and during the flow, the patients suffer from intermittent attacks of pain in the lumbar and hypogastric regions, as well as from a sense of fulness and tension low down in the pelvis. These pains are often quite sufficient to oblige the patient to remain absolutely quiet in her bed or in an easy-chair, because the slightest movement exasperates the sufferings. The pain may be so severe that sleep is impossible; the abdomen is tense; meteorism is present, and palpation is sometimes so painful that in certain women it may produce syncope.

In dysmenorrhœa produced by a lesion in the adnexa, the pain will usually be present several days before the appearance of the flow, and will stop or be less intense as soon as the former is established. Its seat is especially low down in the pelvis, principally over the region of the ovaries, from which it radiates in all directions. Its characteristics proper are confounded with those of peri-uterine lesions which usually accompany those of the adnexa.

When the dysmenorrhœa has a mechanical cause, the pains are sharp, intermittent, and colicky, or more often they are continuous with exacerbations, and may be so intense that sometimes the patient rolls on the ground in agony. These colics often begin before the appearance of the flow and then stop, or they may continue for one or two days, sometimes even during the entire length of the menses. They may progressively increase in intensity according to whether there is an abundant transudation or a retention of the blood.

Apyrexia is complete, excepting when existing peri-uterine lesions undergo temporary inflammation. The flow is very difficult, the blood coming away drop by drop, or containing clots which are expelled after a colic. The flow may also stop for several hours, or a whole day and then recommence. The entire duration of the menses may be prolonged or considerably abridged.

According to the individual, the pains are more intense either before the appearance of the flux or during its presence. They become usually more calm toward the end of the menstruation.

The pains are not always localized in the abdomen and in the domain of the lumbo-abdominal nerves, but they may shoot down the thigh following the track of the sciatic or the crural nerves, and intercostal neuralgia is not rare. Facial neuralgia and migraine are not infrequent. As in amenorrhœa, there may be severe nervous reflex or psychical pains which are either temporary, such as convulsive, hysterical, or epileptoid attacks, nausea, vomiting, etc., or permanent affections, such as sensorial troubles, various forms of paresis, hypochondria, and even insanity in those who are predisposed. Hysteria, which is a frequent complication of dysmenorrhœa,

may also develop under the influence of the latter. As in amenorrhœa, sanguineous transudations may be observed.

Regarding the nature of the flux, it may be said that the blood of the menses is sometimes only slightly colored and mixed with a varying quantity of mucus. Sometimes it is black and mixed with numerous clots; at other times it may have the normal color of menstrual blood, the quantity being increased or diminished.

The flow may be insignificant and sometimes *nil*, so that the physician may find himself in the presence of amenorrhœa and dysmenorrhœa in the same patient. Dysmenorrhœa is consequently sometimes accompanied with either metrorrhagia or amenorrhœa.

If the blood from a patient suffering from dysmenorrhœa be collected and examined, pseudo-membranes will sometimes be found. These membranes are made up sometimes of a simple fibrinous clot representing a real cast of the uterine cavity; at other times the entire endometrium will be found detached, thus forming a pure non-puerperal decidua. These membranes should be distinguished from those furnished by an abortion occurring during the first few weeks of pregnancy.

The following comparative tables borrowed from Auvard may be found of value in making the differential diagnosis:

Membranes in Miscarriage.	*Membranes in Dysmenorrhœa.*
Considerable thickness.	Much less thick.
Great vascular richness.	Slightly vascularized.
Chorial villosities distinctly visible when the piece is placed in water.	No villosities; nevertheless, under water inequalities may be shown, but they are much shorter and much less luxuriant than true villosities.
The presence of the ovum, when it can be found.	Ovum wanting.
Pavement epithelium.	Prismatic epithelium.

The distinction that it is possible to make between the *débris* of miscarriage and that of dysmenorrhœa will indicate that the physician is not dealing with a patient suffering from repeated miscarriage, as some authors have pretended, when in reality it is a dysmenorrhœa (Auvard). For that matter, the regularity in the appearance of the menses and the possible occurrence of the dysmenorrhœa in virgins or celibates render this opinion inadmissible.

Marriage will often cause dysmenorrhœa to disappear when it is due to tardy development of the sexual organs; while, on the other hand, it will aggravate this menstrual disorder if it is dependent upon uterine or peri-uterine lesions.

In cases of dysmenorrhœa sterility is extremely frequent. Ac-

cording to Sims, about half the women affected never conceive, and a great number of the organic lesions which produce this menstrual disorder will give rise to miscarriage.

Diagnosis.

Lumbo-abdominal neuralgia with a painful point over the uterus, which is exasperated by the congestion of the organs during the menses, is about the only disease which might be mistaken for true dysmenorrhœa, and the diagnosis should be made between the periods by discovering the painful points, notably that which has for its seat the junction of the corpus with the cervix uteri.

It is often possible to distinguish whether the dysmenorrhœa is due to a lesion of the appendages or of the uterus. In the first hypothesis, it is infrequent that the physician will not find in the interval of the menses pelvic pains and physical signs of an old, chronic pelviperitonitis or an ovarosalpingitis; and still more, the pains of dysmenorrhœa are more precocious in their relation to the period and have a localization and a type which are characteristic.

In the second case, the uterine colic is quite characteristic. The pains only appear with any degree of severity at the time of the menses and are usually entirely absent during the interval. Direct examination will allow the physician to recognize the nature of the obstacle which prevents the easy flow of blood in the vast majority of cases. The pains may be so severe as to render the woman very low-spirited, and she may desire quiet and solitude. While the pains are at their greatest intensity the appetite is diminished or suppressed, the tongue becomes coated, and the breath has a disagreeable odor; often the patient has nausea or even vomiting.

Tenesmus of the anus or of the bladder is occasionally met with, and certain women subject to dysmenorrhœa have diarrhœa at each menstrual period, which often then takes the place of the habitual constipation. Sometimes the abdomen is so painful that the affection might be taken for the commencement of a general or a pelvic peritonitis; but the pulse remains steady and strong and the temperature is normal. These two elements are a very great help in the diagnosis of doubtful cases.

If there is complete integrity of the genital apparatus, the general health and the antecedents of the patient should be carefully gone over and ascertained in order to discover the cause of the menstrual trouble.

Treatment.

At the moment of the menses, the painful manifestations complained of by the patient may be treated with hot poultices to the

abdomen; a rectal enema containing laudanum, or the bromides, may be prescribed. The tinctures of cannabis indica and of viburnum prunifolium also have their advocates. In cases of dysmenorrhœa complicated with menorrhagia, the formula already given containing hydrastis and viburnum will be found of service.

Enemas containing chloral and the tinctures of valerian, of musk, or of asafœtida may also be tried with success. In well-developed non-anæmic women, when there is no inflammatory process present, viburnum prunifolium is especially indicated. Morphine, either by the stomach or subcutaneously, is to be most strongly condemned in this affection, and we should advise instead of it belladonna combined with cannabis indica, as recommended by Farlow in the following prescription:

℞ Ext. belladonnæ,
Ext. cannabis indica, ... āā 0.2
Ol. theobrom., ... q.s.
M. ft. Supposit. No. x. S. Insert one suppository every night and morning, if necessary.

Antipyrin, according to some authors, should be administered only in those cases in which the dysmenorrhœa is complicated with menorrhagia. However, we have seen excellent results come from the daily administration of from 2 to 4 gm. of this drug in cases of the membranous form of the disorder. Antipyrin may be prescribed alone or combined with the bromides. The following formula represents a very excellent combination of these drugs:

℞ Antipyrini, ... 10.0
Ammon. bromid.,
Potass. bromid., ... āā 5.0
Ext. viburn. prunifol., ... 20.0
Spir. vini gallici,
Syr. cort. aurant., ... āā 40.0
Aq. dest., ... 90.0
M. S. Take a teaspoonful four or five times daily.

For the treatment of dysmenorrhœa in young girls, the following may be found useful in controlling the pain:

℞ Tinct. belladon. fol., ... 5.0
Tinct. opii camphoratæ, ... 10.0
M. S. Take fifteen drops in water as required.

The emmenagogues that we have already mentioned in the section devoted to amenorrhœa may also find their indication in this affection and should be administered a few days before the appearance of the menstruation. The permanganate of potassium, given in the form of pills, in doses of 15 to 60 cgm., is largely employed in England,

and is especially advocated by Ringer, who considers it a precious regulator of the menstruation. The diet and the hygienic condition of the patient during or in the interval of the menses should be regulated according to the particular indications of each case; but such measures can be curative only if the disorder is caused by bad general conditions or by tardy development of the genital organs. The bowels must never be forgotten, a consideration which is often overlooked by the physician, judging from the large number of young women who have always been constipated and who have never taken care of themselves in this respect. As a laxative, saline mineral waters, taken in the morning, especially those containing sulphate of magnesium and salts of sodium, will be all that is required. For poorer patients who cannot afford the luxury of a mineral water a solution of sulphate of magnesium may be used. The following will be found of value as a good laxative in case salines are ineffectual:

℞ Pulv. jalap., ... 10.0
Pulv. rhei,
Oleosacch. limonis, ... āā 5.0
Sulphur. præcip.,
Potass. bitartrat., ... āā 20.0
M. S. A teaspoonful in a glass of water, to be taken in the morning.

In terminating the symptomatic treatment we might say that marriage or pregnancy is often the means of bringing about a cure.

Curative Treatment.

The curative treatment is in the majority of cases surgical, and may vary of course with the nature of the lesion.

Treatment of Uterine and Peri-uterine Lesions.—Progressive dilatation, preferably with Hegar's sounds, negative galvano-caustic applications, incisions of the cervix, repeated curetting, especially in cases of membranous dysmenorrhœa, followed by the intra-uterine application of tincture of iodine or of a solution of creosote in glycerin are also recommended for uterine lesions. The excision of polypi or the enucleation of small fibromata by Vulliet's method and the various operations for correcting the flexions or versions of the uterus, should be performed according to the case, and will usually be successful in curing the dysmenorrhœa if the latter is dependent upon any of the above-mentioned lesions of the uterus.

The peri-uterine lesions, such as perimetritis, ovarosalpingitis, hæmatocele, tumors, etc., which determine the dysmenorrhœa have symptoms special to themselves which will demand treatment. If dysmenorrhœa alone exists, the physician should be guided in his

choice between palliative and radical treatment by the intensity or stubbornness of the disorder.

The gravity of the psychical or nervous symptoms which sometimes complicate dysmenorrhœa, such as epilepsy, hysteria, or mania, has been the subject of discussion as to whether in these cases an artificial menopause should not be brought about. When all apparent lesions of the genital organs are wanting, Battey and Hegar simultaneously, and afterwards Lawson Tait, and after these gentlemen a large number of surgeons, have decided the question in the affirmative, with very different results, and have carried it into practice perhaps too frequently.

Oöphorectomy will cause the dysmenorrhœa to disappear, but not so the other symptoms which are general and due to a neurotic constitution. In such cases the happy effect produced may be only temporary, and the same result has often been produced by a make-believe operation, the action being that of a simple suggestion; and lastly, in spite of the safety of modern surgery, the operation of castration always has the disadvantage of rendering the patient forever sterile. Nevertheless, it counts many brilliant and sure successes, and the dysmenorrhœic accidents are such sometimes that no other interference but this could completely do away with them. Hegar held that castration should be restricted to cases in which a lesion of one or both appendages had been demonstrated by examination; but a diagnosis cannot always be made, and it is still more difficult to appreciate a lesion if the function is not present. On the other hand, a pregnancy in a degenerated woman is not perhaps a desirable thing, as Goodell, of Philadelphia, has suggested. In the presence of these contradictory arguments and of the great variety of symptoms observed in different patients, it is very difficult to formulate a general rule which could be followed in the vast majority of cases. In all cases the question of castration is not to be considered until all the conservative methods of treatment have been tried, and have resulted in failure. The solution of the question will often depend upon a careful and conscientious examination of the given case and an analysis of the rational symptoms, as well as the physical.

Péan considers uterovaginal castration far superior to oöphorectomy, because it more surely does way with the starting-point of the reflex symptoms; and Pozzi, basing his remarks on two successful cases, admits, as does Brennecke, that hysterectomy brings about an atrophy of the ovaries very soon after its performance. It must here be remarked, however, that Grammatikati has experimentally demonstrated, both in rabbits and in the human female, this fact, which Hofmeier had already foreseen, that the ovaries remain in full

physical activity after the uterus has been removed. After oöphorectomy the lumbar centre no longer performs its functions, or at least only automatically, and soon ceases entirely to do so. After hysterectomy, on the contrary, if the ovaries are left in place, not only will the menstrual molimen often be observed (Glaevecke having noted in it fifty per cent. of cases after castration), but what is more, serious troubles of long duration may occur. As a practical deduction from experience, the rule of operation among surgeons of authority requires the removal of the ovaries when hysterectomy is performed in young women. After the menopause, this complementary operation is entirely indifferent. The Fallopian tubes, however, are anatomically a part of the uterus and should always be removed with the latter in hysterectomy for adenoma or cancer of that organ.

The Troubles of the Menopause.

Menstruation ceases, as we have already said, between the ages of forty-five and fifty. The flow becomes less and less abundant, is wanting sometimes, and then definitely disappears without further trouble. This suppression may have, as an occasional cause, a chill or an intense mental impression. When once the menopause has taken place, the mucosa of the genital organs becomes pale, the vulva takes on a withered condition, the hairs on the pubis become white and fall out, while the mammary glands shrink and atrophy. An atrophic process by sclerosis invades the entire female genital apparatus.

This period of transition does not take place without producing certain troubles similar to those which occur at the beginning of puberty. In women who are otherwise in good health, they are slight and ephemeral and disappear as soon as menstruation has ceased; but when a pathological condition exists they may take on a very serious importance.

The disorders of the menopause may be divided into four groups, namely: those occurring in the uterus; those affecting the organs of circulation; disorders of the nutrition; and nervous phenomena.

We will first consider the uterine complications. Often menorrhagia, followed or not by a period of amenorrhœa, or rarely metrorrhagia, is often observed during the last months of the menopause, and afterwards the menses no longer appear. If the woman is affected with malaria or a disease of the spleen, particularly pernicious anæmia, these conditions often give rise to menorrhagia, but when they are properly cared for by a well-directed treatment, the losses of blood will cease, after which the menopause normally takes place.

In the vast majority of cases a metrorrhagia occurring during the menopause is either due to some trouble in the circulatory system, to an endometritis or to a uterine polypus which has not been recognized, or it is a symptom of the beginning of a malignant degeneration of the uterus. This latter fact should never be forgotten, as far too many cases of inoperable carcinoma of the uterus come to the surgeon on account of the neglect or indifference of the family physician when the patient complains of metrorrhagia at the time the menopause might be expected. The same thing may be said with even more emphasis of hemorrhages that sometimes occur with an appearance of periodicity several years after the menopause has taken place.

In the circulatory system, visceral congestions are particularly to be noted. Congestion of the lungs, of the liver, cerebral hemorrhage, hemorrhoids, hæmaturia, a return of the menses, profuse perspiration, or periodical galactorrhœa are to be mentioned as most frequently occurring.

Disorders of nutrition occurring during the menopause are frequently plethora and obesity. The return of extinct scrofulous manifestations or of chlorosis is to be particularly noted. Charcot says that the first manifestations of gout or chronic rheumatism may be observed at this time.

The nervous troubles which are met with are vertigo, palpitations, flashes of heat, and neuralgias, particularly of the ovary. As at the other end of the genital life, cases of nervous pregnancy have been observed which could only be explained by an awakening of the genital sense, and coincident with the commencement of obesity there are certain more serious troubles which may occasionally occur. These are paraplegia, a recurrence or the appearance for the first time of hysterical or epileptoid manifestations; and in the degenerated, or those having an hereditary predisposition, various psychoses appear.

Lastly, menstrual exanthemata often take on a new vigor and may from this time on become chronic. There is a rule in physiology that the menopause marks the end of the genital life in women if it does not her sexual life. Some exceptional facts, however, prove that sterility is not always definitive, as Deshayes has seen pregnancy occur two years, Lemoine three years, Puech six years, and Renaud twelve years, after the cessation of the menses.

Treatment.

There is no general treatment to be directed against the accidents of the menopause, as each one of them presents its own indications.

Nevertheless the chances of the occurrence will be greatly diminished by a proper hygiene and light alimentation, laxatives, exercise in the open air, abstinence from excessive work or of considerable mental tension, not forgetting moderation in indulgence in the conjugal relation.

FUNCTIONAL DISORDERS

OF THE

MALE SEXUAL ORGANS.

BY

CHARLES W. ALLEN,

NEW YORK.

FUNCTIONAL DISORDERS OF THE MALE SEXUAL ORGANS.

INTRODUCTION.

The differential diagnosis between those sexual disorders which are functional and those which depend upon organic change furnishes a subject of great importance, and one which has hitherto been much neglected and consequently is often but poorly understood. The sum-total of human misery which can be attributed, and indeed directly traced, to these functional complaints is astounding. That which is disclosed in the secrecy of the specialist's consulting room forms but a small part of the mental torment which exists in the world because of real or fancied imperfections and weaknesses of the genital functions.

The sexual is the strongest instinct with which man has been endowed. Maintenance of species depends upon the maintenance of sexual desire. Upon sexual hygiene depends oftentimes a continuance of the individual's well-being and happiness. Sexual neurasthenia is of all the forms of nervous exhaustion the most important; but from it must be distinguished the sexual weakness which is but one of the manifestations of spinal or cerebral neurasthenia. When the nervous system is pathologically affected the sexual is frequently among the first of the functions to suffer, and it is in connection with the organs of this system that one of the important nerve centres for reflex irritation is located. In view of the importance of the whole subject and the frequency with which the physician is brought face to face with questions bearing in one way or another upon sexual matters, it is difficult to understand the manner in which some authors have evaded many topics with which practising physicians should be wholly familiar, referring to them perhaps, in the words of one writer, as "ticklish if not absolutely repulsive." Whatever knowledge and skill may bring relief from the suffering of disease and be of benefit to humanity, no physician should hesitate to acquire.

Naturally, distinctions must be made between conditions which result from degeneration and those due solely to degradation, and

sexual perverts must be separated from the sexually perverse; but I cannot at all agree with a distinguished American authority who dismisses the whole subject in a few lines with the statement that "the very contemplation of it is degrading." The scope of the present article will not permit me to enter into many conditions which have the greatest sociological as well as psychological importance, but I wish here to protest against that feeling among writers and readers that he who would remain undefiled must not touch pitch. This unscientific way of thinking has done too much already to retard progress in this branch of medicine.

Impotence.

Definition.—When we speak of impotence in the male we mean that condition in which, for one reason or another, there is an inability to carry out the act of copulation—*impotentia coëundi.*

In his normal state every adult male, during the physiological period of his virility, has the power to perform the sexual act. Impotence implies a lack or loss of this power. It may be due to deficiency of erection, either as regards quality or duration, the erectile tissues of the organ not becoming or not remaining sufficiently distended with blood to permit of a consummation of the act; or there may exist some congenital or acquired state of the generative organs which renders intromission of the penis ineffectual or impracticable. There may be total absence of erection or there may be an entire absence of a virile member, and, though an abundance of healthy semen may be secreted containing fecundating spermatozoa, such a man is not alone impotent but mechanically sterile by reason of his impotence. While in this sense a man who is impotent is likewise sterile, the converse is in no wise true, since normal erection, orgasm, and even ejaculation, may take place in a variety of conditions which necessitate sterility; such are double epididymitis with occlusion of the vasa deferentia, and absence of true seminal fluid or of those elements which render it capable of fecundation. In the same way such eunuchs as have been spared the penis when deprived of their testes are said at times to preserve the power of erection and copulation for several years with the accompanying pleasurable sensations. Hence though sterile they are not impotent.

The broad acceptation of the term impotence, implying an inability on the part of the male to consummate sexual congress, must, therefore, of necessity embrace both physiological and pathological conditions of widely different nature. These conditions may be of temporary duration or they may exist as permanent states of lack of

virility. In the one case the impotence is only relative; in the other it is absolute.

It may be caused by any abnormal physical state which acts as an obstacle to the introduction of the male organ into the vagina, or by disorder of the nervous or muscular apparatus concerned in the mechanism of erection and ejaculation, or by such constitutional disease as impairs the generative function of the individual.

Mechanism and Causes of Erection and Ejaculation.

Since the erect state of the penis enters so largely into the question of potency, it will be proper for us to take up here these questions.

Erection.—While partially under the control of the will, mental efforts alone are not uniformly capable of producing erection, and, on the other hand, the latter may arise in spite of the strongest efforts of will power to repress it.

The chief exciting causes of erection are psychical impressions, and peripheral and central irritations.

Among the first are to be mentioned the sight or thought of, or contact with, women; among the second the various local irritations to which the glans penis and urethra are subjected, as well as those arising from a distended bladder or rectum, and the frictions of clothing and those incidental to horseback and bicycle exercise, not to mention that which may be brought about voluntarily by the subject himself. Among the central irritations we have those of the spinal cord, arising from disease or injury, as exemplified in the priapism observed as an early symptom of tabes; those of the medulla, caused by an asphyxiated condition of the blood, as seen in cases of strangulation, and the irritant effect of certain drugs such as cantharides, muscarin, etc.

The nervous centre which presides over and governs the process of hardening of the penile tissues, and their maintenance in this rigid state until the generative function of the organ has been completed, is situated in the lumbar portion of the spinal cord. Here Eckhardt[15] discovered his *nervi erigentes* which embrace the vasodilator fibres distributed to the vascular system of the penis. These control the dilatation of the arterioles, especially of the corpora cavernosa and corpora spongiosa, permitting an increased volume of blood to enter the organ.

Contraction of the fibres of the accelerator urinæ obstructs the backward flow through the dorsal vein, and this stasis of venous blood

adds to and aids in the continuation of the rigidity; this may continue for hours oftentimes in conditions of satyriasis and diseases affecting nerve tissue, especially that in proximity to or in the cord above the erection centre, and producing priapism.

From this spinal centre, to which the sensory nerves of the penis, prostate, seminal vesicles, bladder, rectum, and contiguous tissues send their branches, there are given off delicate fibres which pass upwards and terminate in as yet an unknown manner in the brain. That the brain acts in an inhibitory manner through fibres passing to the spinal centre is shown in certain psychical conditions of which we shall speak later. Peripheral impressions affecting the special senses of sight, hearing, and smell, may be sufficient to start up this reflex metamorphosis, and a sudden unbidden and distracting thought may enter the mind which instantaneously counteracts all other nerve influence, and flaccidity at once results.

Tristram Shandy would appear, according to Sterne, to have been aware of his own narrow escape through the inhibitory action of these nerves, when, just at the critical moment, his mother had almost distracted his father's attention by asking if he had remembered to wind the clock before retiring. The contraction of the muscles of the penis is partially controlled by will power; and their contraction, which is excited in a reflex manner by stimulation of the sensory nerves of the penis, may serve to augment an erection which has already taken place.

It is important to bear in mind this inhibitory effect arising from mental preoccupation, emotions, fright, fear, and especially lack of confidence on the part of the individual in his own ability to properly perform his part. Its practical applicability will be apparent when we come to consider the psychical and other forms of supposed impotence. Erections are stimulated by a distended as well as by an inflamed state of the seminal vesicles, and while, as is well known, distention of the urinary bladder furnishes the necessary peripheral irritation for the habitual morning erection, it is probable that a well-filled seminal vesicle acts as a normal stimulant to healthy erection.

Abnormal states of this condition are induced by injury of the cervical cord, as Ollivier has shown, and priapism has been frequently observed as one of the early signs of locomotor ataxia. The erection which takes place in hanging is a familiar instance of the effect of injury to the cord in the region of the neck. It has been observed that when injury has occurred to the lower portion of the cord in which the nervi erigentes run, no erection follows from the irritation higher up; consequently after injury to the back, the occurrence

or non-occurrence of priapism may have decided diagnostic significance.

In youthful subjects the passage of a sound into the deep urethra is likely to result in erection, while in infants a disproportionate peripheral irritation, such as may be excited by phimosis, ascarides, bladder stone, or even skin disease of the penis, often results in prolonged priapism.

Ejaculation.—The expulsion of the seminal fluid into and through the urethra calls into play the combined efforts of the nervous, muscular, and circulatory systems. These are influenced in the normal act by the simultaneous working of peripheral and central stimulation, such as has been active in the production of the erection.

It is the ejaculatory centre situated in the spinal cord, stimulated by excitement of an erotic nature and by the irritation of the sensory nerves of the penis from contact with the vagina, which transmits the motor influence to the vesiculæ seminales, causing them to contract and to expel their contained fluid. It is in abnormal states alone that the central stimulation is of itself sufficient to cause ejaculation, in the absence of all local friction. The degree to which the pathological state has advanced may be measured by the diminishing amount of local impulse required to effect ejaculation, and when the latter takes place from unaided psychical impulse, especially in the absence of erection, a serious condition confronts us. The mechanical stimulation of the nerves is a prerequisite to healthy reflex action upon the ejaculator muscles.

The act, while in a measure under control of the will, is governed by motor influences which at a certain period gain the ascendancy and overcome all volition. Still many men acquire by practice such control over the muscles involved that they can delay the emission of semen for a considerable time, and, in order to avoid the natural consequences of coitus, practise withdrawal of the penis just before ejaculation. This practice, all too common, has in many instances led to affections of a more or less serious nature, which will be spoken of hereafter. The mouths of the ejaculatory ducts are directed forward, and after passing from them, the seminal fluid collects in the bulbous urethra behind the compressor muscle. Here the distention of the canal excites reflex contraction of the bulbocavernous muscle, which forces it along the canal and through the meatus in a series of expulsive gushes. At the moment of full erection a swelling of the caput gallinaginis furnishes a barrier to the passage of urine into the urethra as well as that of semen into the bladder. Abnormal conditions which permit the semen to take this unnatural course towards the bladder may result in sterility.

In one case of Keyes' related by Fuller[18] a stone operation had resulted in a cicatrix which caused the mouths of the ducts to open towards the bladder, into which the ejected fluid naturally escaped.

Etiology.

Impotence is in the vast majority of cases unquestionably the result of misuse of the sexual organs and abuse of their functions in natural or unnatural ways. Many instances are found in association with seminal incontinence and depend upon a common cause.

Aside from these etiological factors we find certain forms of cerebral disease; lesions of the spinal cord, implicating the centre of erection; grave systemic disease, especially those attended with cachexia and poisoning by tobacco. The etiology of each different form of impotence will receive separate consideration in the appropriate place.

Classification.

Authorities have not been in accord upon the proper manner of classifying the various forms under which impotence may present itself. The simplest and at the same time most scientific classification is that proposed by the late regretted Professor Ultzmann,[19] under whose kindly instruction it was my good fortune to have passed some time. Following the most pronounced etiological factor in each instance he distinguishes: 1. Organic impotence; 2. Psychical impotence; 3. Impotence from irritable weakness; 4. The paralytic form of impotence.

Organic Impotence.

This depends upon structural defect or morbid condition of the parts, such as malformations, mutilations, anomalies, and diseases of the penis (hypospadias, epispadias, elephantiasis, tumors of the penis, absence of the penis), or of the testes or their associated organs. It may also be due to the existence of some abnormal state which prevents the outflow of the healthy seminal fluid into the vagina. This form of impotence is usually absolute, though like the second form it may be only relative in certain cases.

Hypospadias and *epispadias* may, in giving a faulty direction to the expelled semen, be the cause of a relative degree of impotence which an operation would rectify. The inability to deposit the seminal fluid within the female genital tract alone renders a subject of

either of these deformities impotent, hence only slight degrees of impotence exist in those having full possession of their generative faculties, since, in order to impregnate, it is often sufficient that semen has been deposited in some portion of the vaginal canal, or even within the vulva.

Elephantiasis, as it influences potency, is usually a condition involving the scrotum primarily and only later on implicating in such a manner the virile member itself as to prevent its proper introduction *in coitu*. In advanced stages of scrotal elephantiasis the penis is, as it were, drawn in and hidden by the massive growth, which latter by its size alone would often interfere with proper intercourse.

Tumors of the penis, such as cancer, gummata, and a rare form of horny growth, may be regarded as occasional impediments to successful copulation.

Absence of the penis, though rare, is a congenital condition, instances of which have been recorded by Fodéré,[1] Agnew, Vinogradoff, and others. Impotence is here a natural sequence. In another class of cases it may be an acquired condition, resulting from amputation of the organ, or destruction in some other manner. Eunuchs who have been deprived of penis as well as testes are of necessity impotent.

An abnormally short or undeveloped penis, especially in an obese subject, or an organ of natural length which is interfered with in action by an abnormal growth in too close proximity, as for example a large scrotal hernia, may render impracticable that close approach which is essential to complete copulation. Retraction of the organ has the same result. The opposite condition of excessive size of penis can scarcely be regarded as a cause of impotence, for while the possessor of such deformity might be impotent with one he would probably not be with every woman. In either case if the seminal flow can be projected well within the vulva pregnancy may result, though no actual intromission has taken place. Instances have been reported in which bladder calculi and urethral strictures have brought about such a degree of penile hypertrophy that coitus was out of the question.

Stricture by itself may so impede the course of the semen at the time of ejaculation that it constitutes a cause of impotence.

Displacements and *distortions* of the penis from accident or disease, such as dislocation into the scrotum (case reported by Malinouski); inflammatory deposits in the erectile tissue or in the fibrous sheaths of the corpora cavernosa may prevent intromission.

Gout of the penis has for the time being the same effect. Smyth[21] relates an instance which he considered unique, but Jacobson,[2] Paget,

and others have observed the condition attended with painful priapism.

Calcification of the corpora cavernosa, as well as cicatricial indurations, have also been assigned as causes.

Phimosis of such a degree as to prevent the outflow of semen might also enter as an etiological factor. Before leaving the subject of the penis we should not neglect to mention the possible occurrence of an *anæsthesia of the glans* which might interfere with the development of an orgasm and its attendant emission. *Hyperæsthesia*, on the other hand, may reach such a high development that the mere contact of the glans with the external parts is sufficient to bring on an orgasm and premature escape of semen before entrance is effected.

Pathological changes in the *testicle* and *epididymis* are more likely to result in sterility than in impotence alone. Both conditions, however, are apt to coexist, and in this way atrophy of the testes, tuberculosis, syphilis of the epididymis as well as of the testicle, sarcomatous and cancerous infiltrations, etc., by pressure upon or disorganization of the secreting portion of the organs and their ducts, may occasion impotence as well as sterility. Since, as I believe, one of the important stimuli to erection is to be found in the distended seminal vesicle, sexual desire is decreased and even disappears in some instances of chronic seminal vesiculitis.

Psychical Impotence.

This form is usually temporary and is more likely to be observed in young men and especially those newly wed, though it may extend through a long period of married life. It occurs chiefly in those of nervous temperament, and is frequently an expression of simple lack of confidence in one's ability. The power is present, no organic impediment exists, and still the subject fails, and each new failure only adds to the difficulties encountered in our attempts to rid him of his truly imaginary though practically real impotence.

The function of the inhibitory nervous apparatus is augmented by this repeated non-success, and, unless medical aid or some fortuitous accident intervenes, that which has been till now simply a neurosis depending upon psychical influences may become a more pronounced and more permanent type of disease.

Certain sexual perverts are to be classed as impotent because of the antipathy which they experience for women, amounting to sexual horror when coitus is in question.

Other individuals, whose general health leaves nothing to be desired, give a history of never having experienced sexual desire. They

manifest a coldness towards the opposite sex without feelings of abhorrence and without showing any perverted instincts as regards those of their own sex. Such instances of innate absence of desire are rare. Those which are acquired by mental preoccupation, and otherwise, are more common. When the mind is intensely fixed upon subjects of an engrossing nature such as the solution of intricate problems, or indeed anything requiring concentrated mental effort, genital excitement is in abeyance. This fact was so well known to Grimaud de Caux and Martin Saint Ange as early as 1847 that we find in their "*Histoire de la génération de l'homme*" the advice given to subjects of excessive venereal excitement to engage in mathematical studies.

Impotence induced by brainwork is usually of a temporary character, and can be remedied in a rational manner. Shock, grief, financial reverses, fear, and apprehension are all capable of inducing an impotence of variable, but usually of brief duration.

Absence of erection may coincidently exist. This has been explained as the result of spasmodic contraction of the muscular fibres embedded in the trabeculæ of the corpora cavernosa. Besides the causes already mentioned we find onanism, gonorrhœa, prostatitis, and inflammatory disease of the bladder or testicles. Almost all cases of psychical impotence present a history of excessive onanism, and this readily accounts for the extinguished desire for the opposite sex. So important a part is played by the imagination in all sexual acts that the onanist comes to rely upon extravagant mental pictures of a lewd nature to intensify the pleasure which he derives from his abnormal act. These abnormal psychical conditions may far exceed in effectiveness nature's physiological incentives, and after a period of excess with ever-increasing extravagance and mental excitement all desire for normal coitus becomes extinguished and impotence results.

Instances have been recorded of individuals who have acquired such power over the ejaculatory functions that while all desire for actual intercourse was absent they could by calling up the imagery of certain sexual conditions produce pleasurable orgasm and ejaculation, and this even at times in the absence of erection!

Some of those affected with impotence of the psychical variety do not have it in its absolute form, but being impotent with certain women and under certain conditions, are to be regarded as relative impotents only. Strangely and unfortunately as it may appear, this form of impotency affects many married men who, while they are unable to fulfil the husbandly duties, are quite normal in their sexual powers with other women, or at least with certain ones. This is accounted for in a certain proportion of those marriages by the fact that

love has not entered into the compact, and may not be wholly the fault of the male partner. The highest degree of voluptuous pleasure attending sexual congress is probably to be found where intense love exists upon both sides in a marriage between two normal individuals.

If indifference exists upon either side, or if the wife is of a cold and repelling nature, manifesting a tendency to check amorous advances, there may gradually develop first a decrease of eagerness with which the act is approached, then a disinclination with increased intervals between the acts, and finally an inability to perform coitus when the attempt is made.

Some men manifest perversions of such a nature that they are able to engage in intercourse only in some particular place or when the object of their attentions is attired in some particular manner, or wears at least some especial article of dress, such as shoes, corsets, rustling skirts, or the like.

Paranoiacs are often impotent, and may, as in the case related by Hughes, account for their acquired lack of virility in some peculiar way. This patient stated that "mysterious enemies" robbed him of his semen during sleep, thus bringing about the state of impotence in which he found himself.

Impotence from Irritable Weakness.

Not only is it requisite for perfect sexual union that desire be present and erection occur, but the latter must be maintained for a sufficient period of time to permit of a series of mechanical movements within the vagina, by which a stimulus is reflected to the ejaculatory centre.

By the term irritable impotence we mean the inability to maintain a vigorous and lasting erection until such time as an orgasm naturally occurs; or the premature ejaculation of the semen, perhaps before an entrance has been effected at all or just as the penis is passing into the vagina. The sexual instinct may be strongly developed, the erection itself may be equally strong at first, but at the moment when all depends upon its remaining firm the rigidity suddenly leaves it, and a sense of shame overcomes the man, who sees in such an occurrence nothing but loss of manly vigor and disgrace. The case is, however, not so hopeless as the patient generally thinks. He is usually of a nervous disposition, perhaps neurasthenic, easily excited, and impulsive. There is, as a rule, a history of onanism having been practised with more or less, perhaps excessive, frequency. The passage of a sound discloses a hypersensitive prostatic portion of

the urethra, and the endoscopic tube demonstrates a hyperæmic state of the mucous membrane in this region. It is not, therefore, so surprising that the delicate nerves here situated should respond prematurely to an amount of stimulation which in a man of healthy parts would need to be maintained for a considerable time, and, indeed, added to by stimulation of another kind in order to bring about the same result.

The whole course of the canal may be more sensitive than is natural, but it is especially in the region of the prostate that the mucous membrane is exquisitely tender and often bleeds upon the passage of an instrument.

Oxaluria can in many cases be shown to exist by the discovery in the urine of octahedral, rounded, or dumbbell crystals of calcium oxalate. These are capable of maintaining a considerable degree of irritation, and are in some instances undoubtedly responsible for a certain amount of the sexual feebleness and hypochondriasis, and hence for the impotence.

Uric acid in excess is a frequent accompaniment in these neurotic subjects, and this, too, helps to protract the results of local irritation. Along with these findings of the microscope spermatozoa are often to be discovered, showing that the condition of spermatorrhœa may likewise be present.

If the mouths of the ejaculatory ducts are looked at through the urethroscope, they are found to be patulous, while in health they are scarcely discernible. This would account, in part at least, for the ready escape of spermatic fluid at unnatural times.

A history of preceding gonorrhœal infection, extending perhaps to the deep urethra, can often be elicited. The inflammation set up in the prostatic urethra may be an etiological element to be added to the other causes enumerated, or, in the absence of a history of onanism, may stand alone as the chief factor, in that a period of impotence, usually quite short, may follow close upon a deep urethritis which has been complicated with epididymitis, prostatitis, etc.

Paralytic Impotence.

In this form there is no erection at all. This is the rule; but, not to draw our lines too closely, let us say that a normal erection rarely occurs. There is also an almost complete absence of sexual desire. From whatever primary cause this variety of impotence may originate (diabetes, locomotor ataxia, morphinism, etc.), there is always paralysis of the bulbocavernosi muscles, to whose contraction is due the forcible projection of the semen along the canal of the urethra.

As a result of this paralysis such emissions as occur are of a weak and dribbling character. The whole motor apparatus of the genital tract may participate in the weakness, and the secreting functions may be in a low state of vigor.

Although mention has been made of diabetes and tabes as primary conditions followed by this form of impotence, these as well as other pronounced systemic affections antedating the first manifestations of sexual weakness may themselves have an origin in sexual excesses, onanism, etc.

The diagnosis of both diseases referred to may at times be suggested by the failing powers. The sexual functions are disturbed in one way or another in about fifteen per cent. of all cases of tabes in its initial stages, and when the disease is fully established impotence is present in nearly sixty per cent. The same is true of diabetes in a more limited sense.

Sexual excesses in themselves exhaust vitality by drawing more and more largely upon nerve force. The amount of stimulation must be ever increased to produce the given result, the sensibilities become gradually blunted, perhaps up to a point of complete disappearance, or the power to produce an incomplete erection may persist more as an aggravation than as a source of satisfaction.

In addition to the causes of impotence so far enumerated under the different varieties in this classification, there are many others which we will briefly mention. Injuries to the cord from accident or disease, especially when involving that region from which spring the nerves governing sexual processes, chronic myelitis, etc., are often followed by shrinkage of the genitals in form as well as in function. Diseases of the brain, hemorrhage into its substance, softening of its tissue, or pressure upon it by new growths, and syphilitic affections involving its structure, all may be followed by impotence of pronounced degree. Syphilis, when it does not affect the brain, but produces a marked cachexia, as well as other systemic diseases attended with anæmia and nerve involvement, such as Bright's disease, leprosy, phthisis, etc., often lead to impotence.

There are many drugs possessed of power to decrease or destroy potency. Among them may be mentioned opium, cannabis indica, tobacco, iodine and iodides long continued, bromine and bromides, alcohol, camphor, lead, nitrate of potassium, arsenic,[22] and the fumes of antimony. Dr. Corput, of Brussels, has called attention to the diminution of virile power and complete immobilization of spermatozoids, as shown by the microscope after the administration of internal antiseptics, and especially of salicylic acid. Beer in excess is said to lead finally to marked decrease in virility,

and it is well known that stronger spirits habitually and freely indulged in lead to an impotent state.

Excessive horseback riding, and probably this will apply equally to bicycling, may cause atrophy of the testes, and thus lead to a state of impotence; but such a cause must be of rare occurrence.

Symptomatology.

The symptoms attending impotence are largely those of the concomitant genital defect, often a state of seminal incontinence, or the underlying constitutional disease plus the manifestations of the sexual hypochondriasis, which is almost certain to result to the patient from his knowledge or belief that he is impotent. True or false impotence alike carries with it, from the moment of its discovery, a subjective sense of degradation and depression. There is a peculiarly strong nervous bond connecting the genital organs with the brain and nervous system, and the loss of function in the former is reflected upon the latter system of organs. The man who imagines himself the victim of impotence because of nocturnal or diurnal losses of semen, or of fluid which he supposes to be such, without having had any real indication that impotence is actually present, manifests a train of symptoms quite as marked and distressing as he who is truly a subject of the affection. The symptoms are mostly subjective, for, aside from the observation of abnormalities of conformation, undeveloped organs, etc., hermaphroditism, and those resulting from accident and disease, which are apparent to the eye or discoverable upon examination with instruments of precision, we must depend upon the patient's account of himself for the data upon which to base a diagnosis.

In psychical impotence there are no symptoms justly referable to the genital organs, since the latter are in a sound state.

Prognosis.

This necessarily varies with the form of impotence under consideration. In the organic it is for the most part unfavorable and depends largely upon the feasibility of surgical interference for the correction of the abnormality. In the psychical and irritable forms a favorable prognosis can usually be given; the organs are normal, and desire and the power to produce erection are present, so that treatment directed to the nervous excitability, combined with local and general measures of a rational kind, and supplemented by sexual hygiene, is all that is required to bring about recovery. In the paralytic form

the question is no longer of such ready solution, and in general the prognosis is decidedly bad.

If by appropriate measures the tone of the genital organs can be restored, a favorable outcome can, however, be predicted even in cases in which the condition has been brought about by excessive onanism. Naturally, there must be complete abstention from the habit. Appropriate local treatment and faradization lead not infrequently to gratifying results.

In impotence coming on after the age of forty years the prognosis must be very guarded, and the patient should be reminded that copulative power naturally diminishes after this age, so that a restoration to pristine vigor is scarcely to be expected.

Treatment.

As intimated above, a certain proportion of cases of organic impotence may be remedied by surgical procedure. Most cases falling under the physician's notice are, however, of the class attributed to irritable weakness, there being a history of onanism or excesses, and the prominent symptom being a too precipitous ejaculation. In these the chief indication is the reduction of the hyperæsthesia and superexcitation. To accomplish this, local measures are of paramount importance. They must be carried out with regularity and the most minute attention to detail. As adjuvants to the topical applications which we shall presently consider, we must include tonics, containing probably with most benefit quinine and iron, or such drugs as the particular case may seem to call for; hydrotherapeutic measures, change of air, rest in a quiet country place, etc. In addition to these, we must employ means to excite erection at appropriate stages of the treatment and bring about situations which will tend to restore the patient's confidence in himself and in his returning powers. In the paralytic form the same local procedures are to be employed, in addition to a line of treatment having for its aim the production of erection. The manner of accomplishing this will be spoken of below. Faradization is here indicated, and it is in this form alone that it is especially useful.

We will now speak of treatment as applicable to the different forms more in detail.

Among the abnormalities which will require surgical operation before the impotence which they occasion can be relieved, may be mentioned shortness of the frenulum. Genital hyperæsthesia, leading to ejaculation *ante-portam* as well as to genital perversions, may depend upon this cause alone. Cases are recorded in which there

was even an absence of history of onanism; the premature ejaculation rendering coitus impossible had finally brought on sexual perversions of a homosexual character, and it was only after incision of the frenulum that coitus had been performed for the first time in the normal way.

Adhesions of the penis to the scrotum, luxation of the penis into the scrotum, or of the testicle into the penis, enlargement of the dorsal veins of the penis permitting a too early outflow of blood, deviations of the erect organ to one side as a congenital condition or following injury of the urethra, infiltrations, deposits, or concretions in the corpus cavernosum, hypospadias, epispadias, etc., are conditions which are generally amenable to surgical correction.

In the same way obstructions in the genital area, such as hernias of large size, scrotal tumors, hydrocele, elephantiasis, etc., are capable of cure, and then impotence depending upon them vanishes.

Hyperæsthesia of the prostatic urethra may be maintained by an abnormally long prepuce and disappears promptly upon circumcision being practised. Impotence or, more correctly speaking, pseudo-impotence, results in the same way at times from stricture just within the meatus or from an abnormally contracted meatus, and relief follows meatotomy. If the source of irritation cannot be located at this extremity of the penis, it may be found at the other, and the bladder should be explored; or perhaps the irritation will be found to start from the rectum. Stricture of the urethra in any portion of the canal may require division before the concomitant impotence will disappear.

In any of these conditions, whatever surgical work is done must be supplemented with much from the realm of sexual hygiene, the correction of errors of urinary function, restrictions of diet, etc.

Psychical impotence being purely functional and presenting no demonstrable anatomical changes, requires a somewhat modified course of treatment. Since many cases originate in prolonged sexual desire which has been ungratified, such as that induced by long engagements and the constant association with a *fiancée* or other whose presence can result in nothing but excitement without relief, sexual rest must be enjoined. The first and all important element in these cases is to gain the patient's full confidence, whether the weakness be due to emotional causes, to financial reverses, or merely to failure in the first attempt at copulation, without any tangible cause behind it other than a nervous excitable disposition. This being accomplished, suggestion is the only needful remedy to apply. This is not of necessity to be made during hypnotic sleep, for waking suggestion suffices. The confident statement and assurance of the physician

that full vigor will return, if made impressive, will be a suggestion of sufficient force oftentimes to accomplish the desired result. Naturally, in any form of impotence which has resulted from onanism, it must be a *sine qua non* that this vicious habit is wholly abstained from.

To overcome the hyperæmia and hypersensitiveness of the deep urethra in irritable weakness, steel sounds should be passed, either daily or every second or third day for a time. The size of the instrument must be sufficient to accomplish the object of distention of the canal. Any source of irritation or obstruction in the canal, such as constricted meatus or deeper stricture, must be removed. As a general rule, the sound should be left lying for some minutes in the canal; the less sensitive the urethra the longer can this period be made. Some cases improve more rapidly when a mild galvanic current is applied by means of a metallic bulb attached to the negative pole, which is introduced as far as the prostatic portion and through which a current of mild intensity is allowed to pass for several minutes. A milliampèremeter should always be used, the current being graduated so that no caustic effect of electrolysis is produced. Three to five milliampères are usually sufficient, and still milder currents may be advantageously employed for securing a soothing effect. The positive sponge electrode may be placed over the perineum or held by the patient in the hand, while the current passes for a few minutes, or a large flat sponge electrode may be used over the spinal region. There should be a strict avoidance of sexual excitement during this course of treatment, and in the intervals of the *séances* there should be secured as much genito-urinary rest as possible. Oxaluria, phosphaturia, or other urinary disturbance should be sought out and, if possible, corrected. Sedatives may be of use in allaying spasm or irritation in the canal.

If erotic desires are not readily controlled, the society of young women, the reading of suggestive books, or the contemplation of pictures or witnessing of plays which might excite, should be avoided, while gymnastics, out-of-door exercises, and sports should if possible largely engross the attention.

If the passage of sounds or the use of electricity has not wholly restored the integrity of the canal, any patch of inflammation which remains is best cauterized by the instillation of a few drops of strong silver solution with an Ultzmann deep urethral or similar syringe.

Dittel's *porte-remède* may likewise be employed for this purpose. The instrument is first passed to the point at which the cauterization is to be made, and then a small cacao-butter suppository containing 2 cgm. or thereabouts of nitrate of silver is pushed down through the

tube and deposited in the canal. The pain and tenesmus following this procedure are usually severe, and it is advisable to order rest in bed and the application of cold to the perineum by means of compresses.

Tannin, lead, and like substances can be applied in the same manner. I have recently employed a similarly constructed instrument, which carries the suppository, fixed in its distal extremity, to the desired portion of the canal, where the obturator presses it out. Airol, the latest substitute for iodoform, has seemed to me to possess advantages for use in this way.

A sedative effect may also be obtained by cold applied directly to the prostatic urethra by means of the Winternitz psychrophore, a double-tubed hard-rubber sound, or by a metallic cooling sound constructed upon the same principle. Here we have the advantages of mechanical pressure combined with the cooling effect of a current of water whose temperature has been reduced to 52° F. or thereabout. The jet passing through the inner or male tube is projected against the beak of the outer or female tube, through which it returns and flows away. This stream should be kept up, according to the degree of irritation to be subdued and the results obtained, for from five to eight or ten minutes at each sitting. A similar device can at times be advantageously employed through the rectum, the end of the sound resting opposite the prostatic portion, or a course of rectal douching may be carried out. The ascending cold douche directed against the perineum each morning has also sometimes a beneficial action.

The rectal electric bulb, especially for faradization, gives in some cases very favorable results. The fact that local irritation of the rectum is often sufficient to excite erection must be utilized in certain instances. Another method of producing the same effect is by the methodical passing of cool, highly polished, steel sounds, or the progressive bougie cure. Appliances have been devised for drawing blood into the organ by means of an exhaust pump in which the penis is enclosed. At times these have succeeded well in instances where erections have been feeble and evanescent.

It is probable that a certain mental effect goes with the mechanism. Indeed, so great is the effect of the mind that, in many of these cases, it is only necessary for us to forbid any attempt at coitus, when a placebo will soon act so powerfully that an infringement of our rule will demonstrate to the patient that he is well. I have succeeded in several instances by instructing the patient not to think of having connection for a certain prescribed period, according to the nature of the case, then not to think of coitus at night, but to take advantage of the erection on first awakening to carry out the act.

The paralytic form of impotence resists all forms of treatment.

Spermatorrhœa.

True spermatorrhœa, in which there is a passive escape of seminal fluid in the absence of erection and unattended with the sensations which accompany normal ejaculation, is by comparison a rare condition. Under this term, however, are generally included all varieties of seminal incontinence not depending upon coitus or onanism as the immediate exciting cause of the discharge. The term, therefore, as we shall employ it, embraces nocturnal as well as diurnal incontinence, and the spermatorrhœa of defecation or false spermatorrhœa.

Nocturnal incontinence, pollutions, or seminal emissions, as the latter term is habitually employed, are expressions which convey the idea of an emptying of the seminal vesicles during sleep, attended or not, as the case may be, by erotic or lascivious dreams, by visions of nude women and of amorous situations. There is present in this loss of semen a natural erection and, to judge from the quality of the dreams, the sensations are the same as those experienced in the ejaculation of coitus.

These emissions occur in health with a varying degree of frequency, and it is only when this frequency is increased beyond a certain point, and especially when the erection and sensation are absent, and more than all when the subject's general well-being begins to suffer, that they are to be looked upon as pathological. It is, however, quite consistent with health that an occasional pollution should not awaken one from a sound sleep, and in the morning, while no dream can be recalled, the objective evidences alone make its occurrence known.

Diurnal emissions of semen are of a more serious nature, and they can never be looked upon as normal. They take place in some individuals from very slight causes, which may be psychical or mechanical, or both causes may be conjointly operative. Under the designation of diurnal incontinence should be included cases in which semen containing spermatozoids escapes during the act of urination. A careful examination of the urine in patients giving a history and presenting symptoms which cause such a state of affairs to be suspected, will often reveal the presence of spermatozoa, but it must be remembered that the urine may wash out of the canal the remnant of a normal ejaculation. These cases are for the most part obstinate, and the symptoms produced by this more or less continuous drain are often severe. A chronic posterior urethritis with threads and shreds in the urine is a frequent accompaniment, and prostatitis may exist coincidently or by itself. These conditions produce congestion and ab-

normal sensitiveness of the prostatic urethra, and induce the seminal incontinence in a way which will be entered into more fully in the section on Etiology.

False spermatorrhœa shows no seminal elements in the discharge which is so common a cause for spermatophobia in highly sensitive individuals. This discharge habitually takes place during or just after the passage of fæces, especially when constipation induces straining and the stools are hard. It has, therefore, been aptly termed spermatorrhœa of defecation. It may, however, occur from other than this mechanical cause of pressure upon the deeper glandular structures. The mucous and seminiferous glands, other than the testes, with which the genital organs are supplied, are constantly elaborating fluids whose function is to mingle with the sperm proper, serving to dilute it and probably in many ways to add to its fecundating value and the viability of the spermatozoids. This fluid, derived mostly from the mucous glands of the urethra and prostate, may be passed during sexual excitement or during straining at the close of urination, and is often erroneously looked upon as semen.

The mental suffering engendered by such faulty conclusions upon the part of men of nervous proclivities may be the forerunner of serious symptoms, leading, perhaps, to hypochondriasis, and this without any loss of spermatozoids at all.

To establish and maintain a constant distinction between spermatorrhœa which contains and that which does not contain the elements of life, a microscopical examination would have to be made, not only in every case but at every expulsion of a suspected fluid. Such absolute accuracy is, however, not called for, because we know that it is quite consistent with good health to observe as a result of physical causes an occasional discharge, in which spermatozoa are present. This must be looked upon, when not habitual, as an accident due to phlethora, having little or no significance. If the seminal vesicles become overdistended, and coitus, onanism, or nocturnal incontinence does not come into play to give the necessary relief, it is neither to be wondered at nor regarded as pathological that muscular effort should under certain circumstances force out some of the fluid.

The general rule holds good, however, that evacuation of semen in the waking state, and in the absence of coitus or mechanical irritation, is not consistent with perfect health.

Etiology.

The causes of the various forms of seminal incontinence differ so much from each other that we must consider them separately.

Seminal Emissions.

This is the commonly employed designation for losses of seminal fluid during sleep, which process is a physiological one in all normal human males during the period of their active sexual life, provided the seminal vesicles are not kept in some other way from distention. So long as they remain within certain bounds of frequency, and are limited in their effects to a promotion of the individual's well-being, they concern us only in an incidental way. From the moment, however, that they become frequent and are followed by such general symptoms as languor, dull headaches, inappetence, neuralgic pains, and signs of genital irritation, they pass from the realm of physiology into that of pathology, and we must seek out the causes which have dominated this change. Chief among them will usually be found onanistic practices. We must not be too hasty in our conclusion that because nocturnal pollutions are, as they seem to us, abnormally frequent in an individual who gives a history of having practised self-abuse, the former is to be regarded as a pathological process depending upon the latter as the chief etiological factor. The frequency with which emissions may occur in perfect compatibility with good health varies within very wide limits, and just as one individual may, by reason of his greater sexual vigor, practise coitus at intervals which would be disastrous to another, so may nocturnal losses occur with equal frequency in two cases, being physiological in the one and pathological in the other.

It is, then, more the effect upon the general health which must guide us than the number of days which intervene between the emissions. The normal pollution takes place in response to a well-established law of nature. When unnatural stimulation is supplied to the generative organs, by allowing the mind to dwell upon suggestive thoughts, the eye to rest upon immoral pictures, the ear to lend itself to lewd and lascivious song and story, then that which was previously a throwing-off of a normally accumulated secretion at necessary intervals, becomes an irritable expulsion of an over-secretion due to unnatural excitation. The first process should give a feeling of relief and benefit; the second reacts upon the general system, and by a combined local and mental effect may lead to the most deplorable consequences. No time limit can be set upon healthy nocturnal incontinence. Some men in perfect health and continent very rarely have emissions. Others in apparently equal physical condition will have an average of one emission every week or ten days. Much must necessarily depend upon the amount of sexual excitement which in-

fluences the secretion of the various fluids by the seminiferous glands in the different cases.

When we pass to a consideration of strictly abnormal emissions during sleep, many causative factors present themselves, and we recognize the tendency on the part of the ejaculatory organs to be excited in their functional activity by a variety of irritative agents in both a direct and a reflex manner.

As we have already stated, onanism is undoubtedly one of the most potent causes of exaggerated incontinence; and still, while the habit is being vigorously pursued, emissions do not take place with any marked degree of frequency, simply because the vesicles are kept emptied. If, as sometimes happens, pollutions occur as one of the symptoms of a grave constitutional disorder, such as disease of the spinal cord or brain, epilepsy, etc., their frequency may not be markedly decreased by the fact that onanism or coitus is being regularly practised.

Nervous exhaustion, debility, anæmia, and deviations from health which bring about disturbances of the body's nutrition and of its reflex centres, act as predisposing causes of seminal incontinence. Heredity no doubt is responsible for much in this connection, by its influence upon the development both of nervous disorders and of vicious sexual instincts and practices. In the family history of sexual perverts there is usually to be elicited an account of insanity, epilepsy, nervous disorders, alcoholism, or sexual inversion itself, as this term is intended to be understood by Westphal. Charcot and Magnan[1] also regarded many of these states as evidence of hereditary degeneration. Chevalier is undoubtedly correct, however, in his division of these cases into two classes, one belonging to an *inversion malady* and the other to an *inversion vice;* and this classification may equally well be applied to onanism as to other perverse sexual acts.

There is another and perhaps stronger argument in favor of the transmission of vice of sexual function, and that is the frequency with which we see the son inherit the father's peculiarities and vices of sexual conformation. There is no valid reason why the genital organs should be exempt from the law which governs inheritance of trait and disposition, but attention has been called to this region of the body much less frequently than to others by those who have written upon these subjects.

Just as a parent may transmit hypospadias (I have in mind a father and three sons, all with the same degree of this deformity), so may he hand down as an inheritance a sexual organization of extreme sensitiveness or irritability and a tendency to those conditions and habits which lead to functional derangement.

Incontinence of urine in the youth is often a forerunner of incontinence of semen in the adult, and many instances in my case books attest the fact that "wetting the bed" as a child was a failing of one of the parents as well.

Gonorrhœa favors the occurrence of spermatorrhœa to a slight degree by the continence it necessitates, and to a greater degree by the congestion of the urethra which it causes.

In many instances a history of an uncured urethritis will be given, and appropriate methods of examination will disclose muco-purulent shreds or gonorrhœal threads, in which gonococci can still be discovered.

Other forms of local irritation may act in much the same manner; thus herpes preputialis, the retention of smegma behind the corona until a balanitis has been established, scrotal eczema, fissure, and hemorrhoids have all been advanced as causative agencies in the production of spermatorrhœa.

Onanism.

This term is preferable to that of masturbation to express autosexual indulgence, because the latter, derived as it is from *manus* and *stuprare*, implies that the self-pollution or defilement must be accomplished by hand. Such a word conveys an inadequate impression of the various acts which should be covered by a general or generic term, which must include many deviations from natural and complete coitus in wedlock, as well as sexual intercourse made incomplete by withdrawing the penis before the semen is emitted; coitus in os, inter mammas, etc., mechanical frictions variously applied, and even a species of mental or psychical onanism in which no mechanical friction at all is required, the subject relying upon the imagery which he conjures up to effect orgasm and ejaculation.

The latter form is very unusual, but in most cases a central as well as a peripheral irritation is at work, and the psychical enhances the mechanical effect.

Another reason for giving the preference to the term onanism is that if it be true that Onan, the son of Judah, was the first to put into practice a habit which has become so universal and has brought so much misery into the world, his name deserves to be perpetuated.

It is unquestionably a most ancient, though it cannot be considered an equally honorable, custom. Its practice is degrading, dishonorable, and if persisted in, disastrous. Though often existing as a symptom of disease, centrally or locally established, which impels to the act, it is more commonly a voluntary practice which has been acquired after the age of consciousness of right and wrong. The boy

is usually taught by an older companion, more rarely at an earlier age by a nurse, perhaps with the view of quieting the child in an easy way by manipulation of the genitals, perhaps from motives of pure perversity. Spontaneous masturbation may occur in quite youthful subjects. Heyward Smith has observed it at the age of two years, and I have myself seen a boy of about three who if left to himself would manipulate his small-sized penis almost continuously and with evident pleasurable sensations, crying and struggling when restrained. In such cases there is usually a local source of irritation, such as that supplied by an adherent or tight prepuce, retained smegma, or irritation about the anus. These have their counterpart in those instances occasionally encountered in adults, who give way to an inordinate desire and masturbate again and again, often in quick succession, without securing the relief sought for by their act. While such excessive onanistic acts, when habitual, must be looked upon as psychological in the main, there are still some which are symptomatic of local or general disease and are resorted to in order to quell unusual sexual cravings induced by seminal vesiculitis or other local process, or are the exponents of brain or nerve lesion. There has been a decided tendency on the part of some authors to minimize the evil effects of onanism in youth. The promulgation of such views is calculated to do good in one sense and harm in another. Coming as they do from those whose wide experience entitles them to speak, they partially counteract the evil effects of that species of quack literature which has a decided tendency to frighten subjects of youthful error, who would be more injured through the horror inspired by the lurid descriptions of "lost vitality" than they would ever be by the direct result of their perhaps thoughtless acts. It is the morbid brooding over the habit fostered by these pernicious pamphlets, which are put into the hands of every schoolboy throughout the land, that so often leads to melancholia in those already mentally weak or nervously predisposed. That concerted effort is not made by educational and philanthropic institutions to stamp a heel of condemnation and annihilation upon the head of this insinuating vampire, the distributor of obscene and quack sexual literature, is a reproach to our twentieth century advance.

While too much mystery is thrown around the sexual function and the whole subject of generation, and youthful curiosity and thirst for knowledge are left unwisely to be appeased by partial truth from those ill-fitted to instruct, still I would not advocate indiscriminate attempts to teach very young children. Examination of first classes in physiology in the public school shows how ludicrously erroneous is the knowledge most young children are capable of acquiring in the sim-

plest matters of digestion and circulation. The subject of the sexual functions would not be mastered, but, instead, curiosity would be excited concerning matters upon which the mind had hitherto dwelt but in a passing manner. Up to a certain point, the simple rule, "Hands off," without explanation, will be more efficacious. Few children require further information than "that it harms the grass" to cause them to obey the "Keep off" notice in the park. They do not have to be told how the seed germinates, nor enter upon the study of botany until later. A certain amount of harm has been done, it seems to me, and advance in these matters has been retarded by writers of legitimate medical literature, who treat of self-abuse as something in which all boys indulge at one time or another as the natural initiation into their sexual life, and which is not so harmful as it is reprehensible.

Onanism in Animals.—In talking at various times with keepers of the animals in zoological gardens, I have learned that almost all animals in captivity are given to onanistic practices. This is especially true, as is well known, of the monkey tribe; and while they at times seriously undermine the health by excesses, some have to be killed for the sole reason that the almost constant practice renders them unfit for purposes of exhibition. The handsomest bear ever seen at the Central Park menagerie, I am told, had to be shot on this account. Likewise an old baboon, who was so perverse that he would wait until he had a large audience of ladies before he would begin—a seeming example of exhibitionism. Several have told me that lions made an exception to the rule. I hope this is true. I like to think, and know that I am justified in thinking, that among boys there are the exceptional "lions," either through innate nobility of character or deserving of the distinction by reason of their abstention.

Causes of Injury in Onanism.—In just what manner onanism causes more injurious effects than follow functional activity taking another direction, is still an undecided question. Some have attributed the consequences to repeated nerve shock; others to the drain upon the system from the loss of so highly vitalized a secretion as the semen is known to be.

That a reaction upon the nervous system takes place differing from that which results from normal coitus indulged in to an equal extent, seems reasonably certain. The frequency of the act is apt to be much greater than in coitus, due to the two elements of constant opportunity and non-dependence upon a second party, except in the rarer mutual or reciprocal form.

The age, too, at which the habit is first formed and most vigorously pursued is one of extreme delicacy of tissue in an active state of

growth and metamorphosis. These susceptible and tender structures are most prone to suffer injury by too great a call upon their activity, and the nervous system as a whole, in common with glandular organs, becomes over-stimulated in an unnatural manner and at an unnatural time of life. Too great strain put upon immature organs in progress of development may result in infantilism or stunted growth, and this is occasionally seen in an arrest of development in the genitals following inordinate manipulation.

If we turn to the female sex for assistance in forming our conclusions, we are led to discard the idea of injury from frequently repeated nerve shock so far as the adult is concerned. Women, as is well known, may perform onanistic as well as copulative acts many times in quick succession and continued over long periods, without suffering in anything like the same degree from the evil consequences so constantly observed in the male. Nor can we attribute the results wholly to loss of semen, since similar derangements follow at times infrequent losses of this fluid.

It must be that the knowledge of wrong-doing, the consciousness of unmanly and degrading action, and the fear of those consequences which in reality do supervene, have much to do with the fact of their development.

In the habit as it is usually observed there is a psychical effect of pronounced intensity, the *libido* is long protracted, the imagination is injuriously stimulated and strained to overcome the reality. This is more pronounced in that form of onanism which is purely psychical, in which the subject relies upon memory pictures and by an intense concentration of mental effort brings on scenes and situations which result in ejaculations.

Another important element is that mentioned by Schrenck-Notzing[3] —the destruction by onanism of the sexual relation to woman, an attack upon the most powerful natural instinct at its very root. Or, as Krafft-Ebing[4] so well puts it: "It injures the whole sexual foundation, the basis of all ideal activities; it extinguishes the fire of sensual feeling, the most powerful incentive to the putting forth of strength in both individual and social existence in the world of beauty and morality."

That there are various elements which enter into the question seems reasonably certain, from the fact that onanism begun later in life or by the practice of "withdrawal" is attended with symptoms pointing to its injurious influence. The latter is in reality the original form of self-abuse as practised by Onan, judging from the statement contained in the ninth verse of the thirty-eighth chapter of Genesis.

Onanism is undoubtedly more prevalent in institutions where boys and even men are confined together, living in possibly not the strictest hygienic surroundings, and where they are subject to evil precept and example. Thus, we find a prevalence of onanism among the inmates of prisons, schools, reformatories, asylums, and among seamen thrown together on shipboard during long voyages. Krafft-Ebing says in many schools "it is actually cultivated," whatever he may mean to imply by this astounding statement. It is likewise very common in asylums for the insane, idiotic, and mentally defective. In this class of patients, however, it is often practised as a species of tic, being more or less automatic, without the association of psychic ideas. That the act conveys sensations of pleasure to the minds of these creatures is evident, and that in some there is a sexual excitement produced by the sight and contact with nurses and others of the opposite sex, is indicated by their actions. This automatic pulling and friction of the genitals occurs at a very early age in some imbeciles and idiots, and, as we have already seen, in normal children, too, at times. Imbeciles are said to show this tendency much less than idiots, but after puberty, when an instinct for sexual gratification develops, they become much greater onanists than the latter.

Onanism may be symptomatic of genital hyperæsthesia and may result in abnormal sexual desire, satyriasis, leading to rape, murder, etc., or in perverse sexuality, leading to homosexual acts and exhibition. Indeed, contrary sexual feeling would often appear to be engendered through onanism. It is most important to differentiate between perverse states which are thus acquired and those which are congenital. Onanism will be present in both, but it may throw light on the question if it can be shown at what period the habit began. Probably idiots suffer less bodily harm from their constant practices because the psychical element is lacking. They feel no after-sense of shame, and do not brood over the habit nor make efforts to subdue it.

Early Symptoms.—Onanism is not a disease, but the great importance which I attach to its early discovery and control leads me to enumerate certain manifestations by which its votaries and victims may be detected.

Altogether too much false modesty and perhaps family pride have tended to keep hidden this prevalent and pernicious habit as it affects young children. Even with the concurrence of the family physician, parents are too loath to institute sufficiently searching investigations. This indifference may permit the growing child to continue the suspected habit for years. Teachers, too, should be more keenly alive to the possible disastrous outcome, and in dealing with the subject and

the individual they should not regard the one as a moral cesspool or the other as hopelessly degraded. It is to be hoped that the coming century will bring more wisdom in this respect to the moulders of human clay than has been shown in the past, and that unnaturally close friendships in the school and social circle, especially between boys of unequal age, will be guardedly watched over, that signs of effeminacy will be investigated, and that the diagnostic features which we shall describe will aid, at least in a measure, to cast or confirm suspicion and lead to measures for the repression of the vice.

The immediate effects of self-indulgence in young children number among them circulatory disturbances of both motor and sensory nature, irritability, insubordination, and outbursts of inexplicable anger. Besides these manifestations there are usually a decided bashfulness and reserve in society, averted gaze, and lack of manly bearing. There is, too, a tendency to avoid company or the joining in youthful sports, but rather to retire alone or with a single companion, upon whom the suspicion of being an accomplice should rest. In study hours there is dulness, drowsiness, preoccupation, faraway gaze, and lack of application, with often pronounced weakness of memory and absent-mindedness.

Later Symptoms.—After a variable period of indulgence there may occur a train of bladder symptoms, such as incontinence of urine, spasm of the compressor muscles of the urethra, and, still later, congestion of the deep urethra, attended perhaps with congestion of the colliculus seminalis, urethritis, prostatorrhœa, seminal incontinence, irritable weakness, and, finally, impotence.

Among the objective signs are to be found flaccidity of the penis, relaxation of the dartos, enlargement of the scrotal veins, all combining to make that pendulous state of the testicles which often results in much mental disturbance. In beginners, as well as later, the lips of the meatus may be red and inflamed, while the anterior urethra is pale.

Among eye symptoms may be mentioned photophobia, pressure, pain, or spasm in the lids, and neurasthenic asthenopia, with diminution of vision.

Mental Symptoms.—Onanism is capable of affecting the mind most injuriously, inducing a loss of resistive power,[24] and the weakness which originated in over-indulgence may pass into such a pathological state that the instinctive automatic act becomes entirely subsidiary to the brain affection. A nice distinction must often be made between onanism because of mental weakness or actual brain lesion, and that which has been practised until mind weakness has resulted. I have recently observed an instance of melancholia in a young man

as a direct result of excessive onanism begun at an early age. The tendency here, however, was towards insanity by inheritance from both branches of his family. Such hereditary predisposition, I believe, will be most usually found to account for such a pronounced effect upon the brain in early life. Mental weakness is probably a much more frequent result, and, in a slight degree, it surely is quite common.

The statistics of Sweden and those of several German observers show that from 1.2 to 3.7 per cent. of cases of insanity admitted to the asylums are due to onanism, and, according to Ellinger's statistics, this is an accessory cause in about twenty per cent. of instances. The very important point is, however, made by Krafft-Ebing that in almost all cases of insanity due to onanism there is predisposition by heredity, and that while in the thirty-one cases he had observed onanism had been practised from early childhood, in three only did insanity develop before the fifteenth year.

The approach is heralded by an unusual disposition to keep apart from associates, to neglect duties, and to become uncommunicative. There is usually, too, hypochondriasis, alternating with irritability, the subject sitting perhaps for hours with the head bowed down, and at other times showing peevishness and outbursts of temper without adequate cause. Ideas of grandeur, conceit, and persecution, with hallucinations, may follow quickly, and attempts at suicide may be made, often taking a theatrical turn. Onanistic insanity, according to Peretti,[24] shows sudden changes, and while there are phantasmas of all the senses, olfactory hallucinations are frequent, and impractical plans are apt to be formed for the future improvement of humanity. These, according to my own observation, often have a direct or indirect connection with onanistic acts. In one of my cases the subject believed himself to be the only perfect man since the time of Christ, and that he had a mission to perform in saving young men from bad influences and the evils of self-abuse.

The very preponderance of the habit over efforts of the will power to throw it off must be looked upon as an evidence of cerebral disease, and, as Schrenck-Notzing justly says: "Memory pictures cultivated by onanism may become imperative conceptions, and force the individual's sexual impulse into a perverse direction. Excess, too, leads to spinal and general neurasthenia, and seriously injures the mental development of the individual." In those hereditarily inclined or neuropathic, the symptoms follow each other with a greater intensity, and the progressive loss of will power and early development of psychoses is noticeable.

Prognosis.—The outcome in any given case depends upon the du-

ration and extent of the habit, the age at which it was instituted, the presence or absence of a neurasthenic state or a psychosis, and whether the latter is cause or effect. In all cases in which the psychical element is absent, the prognosis is good. Marriage or regular intercourse suffices to correct the habit in most instances. In some cases of long standing it persists after wedlock, and either onanistic practices of one kind or another are continued—another victim being added in the person of the wife—or the union has an unhappy outcome in one direction or another.

The great majority renounce the practice so soon as they begin having regular sexual intercourse, and many do so long before marriage and without the natural substitute.

The prognosis, then, for most cases is good. If the practice be persisted in, impotence may result, or at least such a blunting of the sensibilities that a full and proper enjoyment of subsequent marital intercourse is out of the question.

Prophylaxis.—The lesson comes to the child in most instances from an older boy. Hence I would suggest that the lines of prophylaxis should be laid down in such a way as to embrace the aid of the youth who has reached or is approaching years of discretion, and cause him to do missionary work among younger boys. These subjects are discussed freely among boys, and if the older ones who have, perhaps, been taught something of sexual physiology and have had wholesome ideas inculcated, are encouraged at every opportunity to say a word against the practice, much good might result. I have been surprised to see the practical results in a small way from such a plan of action. I number among my patients who have renounced the habit and been cured of their symptoms several manly little fellows who have thus made their influence felt for good. I would have organized in every boys' school a corps of chastity, composed of the older boys. This plan would first of all make the very best excuse, and so far as I know offer the best method of correcting the habit in the select few who composed the corps and received suitable instruction. They in turn would be expected to raise a voice of condemnation whenever possible, and point out to the younger boys the folly of their ways. Much tact and discretion would naturally have to be employed in carrying out such a course, but I see no valid objections to it.

Treatment.—Much can often be accomplished in a local way towards the correction of the habit in early life, as by the surgical removal of a tight or elongated prepuce, or by the correction of any local source of irritation, such as a collection of preputial smegma or thread worms.

In subjects too young to be influenced by any attempts to elevate the *morale* or to act upon them by suggestion, some form of mechanical restraint must be applied, as by binding down the arms in such a way that the genitals cannot be reached by the hands, or by placing over the parts a cage-like apparatus, securely fastened; or, as recommended by Fournier, a ring may be inserted into the prepuce near the frenum and worn continuously. The pain occasioned by manipulation soon leads to a relinquishing of the attempts. The latter device is especially useful in the automatic form, in which onanism occurs during sleep, the subject awakening perhaps to find the act completed or completing it in half-waking dazed condition, in which the will power appears to be in complete abeyance. If œdema occur while the ring is worn, it will indicate that the habit is being persisted in. Before fastening the hands and arms it must be ascertained that the orgasm is not brought about by movements of the body against the bedding. One of my patients who had been a persistent onanist assured me that he never used his hands, but always brought on the orgasm by lying on the belly and going through certain motions.

Another though less effective plan is to make blistering applications with cantharides or carbolic or other acid, used naturally with care, first to one side of the organ and, as this is healing, to the opposite side; care must be taken that this is persisted in long enough, or the habit will be resumed. In the psychical form none of these devices may avail.

In older children the *morale* must be improved and the subject's confidence secured. Suggestion may then be made, usually without hypnosis, or with it as in a case reported by Bernheimer, in which a lad of eight years was cured by this means. Effects can often be obtained in partial hypnosis, and I have employed the method at times with seemingly good results. In all cases the nerve tone can be strengthened with advantage, since the evil results are so preponderatingly psychical. A certain amount of suggestion should go along with any drugs which are employed. The patient should be impressed with the belief that the remedy will strengthen the nerves and will power, and thus he will be aided to withstand temptation, and the desired benefit will be the more likely to occur.

Speaking of suggestion, Schrenck-Notzing[23] says: "No other method can be compared with therapeutic suggestion in rapidity and certainty of action; psychical therapy in the waking state often does not succeed where hypnotic suggestion is successful. . . . It is destined in the future to play the principal rôle in the treatment of

onanists, while former methods are to be employed only for the sake of completeness."

General measures, such as healthful exercise, gymnastics, the avoidance of stimulating food and drink, especially of alcohol and this more particularly at night, are useful. All those things which tend to excite sexually are to be avoided; such are lascivious books, pictures, plays, and lewd company.

Hydrotherapy comes in for a goodly share of usefulness. Morning cold plunges, shower baths, sprays, cold douches to the spine and locally to the genitals (only in the morning), together with general frictions of the surface, especially with hair mittens, are all measures of great utility as adjuncts.

Among useful sedative drugs may be mentioned the bromides, camphor, especially monobromate of camphor, which may be administered at bedtime.

The patient should arrange to be awakened after several hours' sleep, to enable him to empty the bladder and thus minimize the chances of erection and genital excitement. Seven or eight hours should be the maximum devoted to sleep, and the earlier the patient is up the better. Tobacco should be used, if at all, in great moderation.

Marriage should never be advocated by the physician nor entered upon by the onanist with the object of finding in it a cure for his condition. Marriage is too sacred an institution to be prostituted in such a manner, and, aside from any other sentimental consideration, one should think of the detestation in which a man would hold himself who would thus abuse a copartnership supposed to be entered into with sacred obligations and high ideals. On the one side, the party to the contract fulfils these requirements, while on the other there are but selfish therapeutic aims.

Sexual Excesses.

Onanism is not the only form of self-abuse. Misuse of the generative function in various ways may induce spermatorrhœa, and excessive coitus is one of the most frequent. It is a safe rule of guidance for the individual that so long as a feeling of well-being follows cohabitation, so long as the act is succeeded upon the same and the following day by a sense of relief, buoyancy, greater brightness of mind and inclination to work, the act is not being repeated too frequently. When, however, the opposite of these effects is noted, and especially if the ejaculation begins to occur too precipitously, it is an indication that the frequency of the act is too great.

Men differ very greatly in their virile powers, and excess must necessarily be a relative matter, depending upon the individual capability. We must look upon all abnormal stimulation, which calls forth repeated and long-continued erection, ultimately leading to hyperæmia of the urethra and irritable weakness, as akin to sexual excess, in so far as it induces the conditions necessary for spermatorrhœa to become established. Along with the changes in the canal itself, there is found to exist a too great excitability of the reflex centres in the brain and cord, which, when combined with an irritable condition of the efferent nerves, tends to induce incontinence of semen in its different manifestations. In adolescence, especially, sexual excess may be the only cause to which we can attribute a given attack of spermatocystitis. The various methods adopted by the libertine to prolong sexual excitement often have the same effect. Once firmly established, this chronic vesiculitis is most apt to determine an excessive degree of onanism, which in turn leads to one or the other forms of seminal incontinence. Catarrhal prostatitis is likewise aggravated by excess *in coitu*, which may eventually lead to false if not to true spermatorrhœa.

The opposite condition to that usually understood by the term excess, *i.e.*, restraint, continence, excitement without gratification, sexual stimulation disproportionate to the physiological relief afforded by normal nocturnal emissions, may have much the same causative influence in bringing about a state of incontinence.

One who continues to indulge in the mental excitement induced by impure thoughts, aided perhaps by improper reading and the contemplation of suggestive pictures, may be guilty of a psychical onanism in which the orgasm is, as it were, simply postponed until the time pathological pollution takes place. Highly excitable and nervous individuals, often belonging to the class of students or other brain workers, become easily alarmed by the frequency of these discharges, and, even when the latter are purely physiological, seek medical aid. Such subjects are, as a rule, readily persuaded that their vitality is rapidly being lost and are not easily convinced of the true state of the case. Falling, as so many do, into the hands of charlatans through the class of literature which these designing pretenders are constantly distributing broadcast, they are encouraged in this belief until their condition is rendered truly serious, and the conscientious physician to whom the patients afterwards apply has a difficult matter to set them right as regards the outcome.

Onanism may be taken up with the faulty idea that in practising it chastity is being preserved; thus the fact of remaining without car-

nal knowledge of woman is responsible for the functional disorders which the psycho-mechanical substitute engenders.

Lallemand [20] claimed that compression of the seminal vesicles and prostate, when constant, caused frequent pollutions. Prolonged horseback exercise and long courses on the bicycle, particularly in the case of ill-fitting saddles, may have such a result. Excessive bare-back riding forms part of the routine through which, according to Hammond, the Pueblo Indians put the member of their tribe chosen to become a *mujerado*, or the one who plays the passive part in the pederastic practices which constitute a feature of their ceremonials. Masturbation is practised upon the victim many times a day in addition. Finally sexual desire and all inclination for masculine pursuits are lost, and the type changes to that of the woman; the effect being somewhat similar to that resulting from castration in the making of eunuchs. There is here a veritable loss of manhood, brought about intentionally and with a definite object.

As an illustration of the occasional evil effects of literature, even when the writings are of a truly scientific nature and intended for medical men, I would refer to a patient of Krafft-Ebing, who was led through lascivious interest to read "Psychopathia Sexualis." The description of cultivating mujerados excited him so intensely that he masturbated five times within two days, thinking of himself as a presumptive mujerado. The good effect of such reading is shown in the same patient's history, for, led by the work to consult its author, a course of treatment was instituted which resulted in great improvement. Many of the conditions being physiological, psychical, or wholly under the patient's will, if the latter can be brought to bear properly upon the condition, a cure may be effected by a species of auto-suggestion.

Both extremes, then—excessive coitus and prolonged continence—must enter into the causation of seminal incontinence.

Local Irritation.

Besides these general considerations, we must take account of the many local sources of irritation which result in loss of semen at unusual times and in unnatural ways. To enumerate them all would necessitate the presentation of a list of disorders peculiar to the pelvic cavity. Starting at the meatus urinarius and proceeding inwards, any constriction or inflammation may excite to spasmodic contraction of the seminal vesicles and the determination of pollution. A tight prepuce or frenum may be at fault, or the point of irritation may lie in the bladder neck or within the bladder cavity. Prosta-

titis, urethritis, cystitis, vesiculitis, may each be the exciting cause of nocturnal losses. Emissions often occur with frequency in gonorrhœa, and the vesiculæ seminales may take part in the inflammation, the discharge showing the darkened discoloration of hæmospermia.

A uniform admixture of blood with the semen is due at times to a chronic spermatocystitis attended with much hyperæmia. When the fluid ejaculated is seen to be principally blood, it is because the seminal bladder has been called upon to discharge its contents at such short intervals that finally its walls have contracted upon themselves, as it were, and delicate vessels have become ruptured. Anything which causes prolonged congestion, either active or passive, of the seminal vesicles, whether it be lying long upon the back in sickness, overdistention of the vesicle from accumulated sperm in states of continence, pollutions being rare, or excessive bicycle exercise with undue pressure upon the perineum, may bring about a hemorrhage sufficient to cause a rusty appearance of the whole spermic mass.

Jamin [25] has written upon non-inflammatory hæmospermia, and thinks in some instances the sudden and complete emptying of the seminal bladder may result in the production of a vacuum, which of itself determines small hemorrhages into the cavity.

Spermatic colic, following long retention of sperm, which has become thickened, in congested vesicles, with the possible formation of gritty masses and even calculi, is productive of hemorrhage, occurring as streaks of blood through the semen. In acute inflammation of the seminal bladder pus may be present as well as blood, and the contraction of the bladder walls may occasion pain. Phimosis may, by reflex action, be the irritation in spermatic just as it often is in urinary incontinence, and an operation may give as happy results in the one as in the other condition.

Other sources of nerve irritation about the sensitive regions of the glans, meatus, and prepuce are often found to act in the same manner. Posterior urethritis, prostatitis, and inflammations of the testes, epididymis, vas deferens, and neck of the bladder, in so far as they have the same effect, are to be regarded as causes of incontinence. I have no doubt that a congenital narrowing of the urethra, in some portion of its extent, is an occasional cause of incontinence of urine in early life. In very many instances this is overlooked, because of an unfounded prejudice against exploration of the urethra and the passage of sounds in the very young. When the child passes into his *vita sexualis* this irritation still existing finds its reflection in hyperexcitability and frequent pollution. It is not an uncommon occurrence in my prac-

tice to obtain in cases of pollution a history of preceding urinary incontinence, and then to discover some local source of irritation.

Symptomatology.

That the symptoms should be manifold in so comprehensive a condition as spermatorrhœa must of necessity be, under our present division of the subject, is self-evident. Not only must they vary according as the incontinence is nocturnal or diurnal, with losses occurring only occasionally or so often as to be almost a constant drain upon the system, but also there is that great difference in the nervous organization and sensitiveness of different individuals to be considered and taken into account. Almost all instances of true spermatorrhœa have passed through the transition stages of abnormal nocturnal incontinence induced by excesses in onanism or in some form of sexual indulgence; diurnal losses, first at stool or due to some other mechanical influence, and then becoming more frequent and no longer depending upon an erect state of the organ or mental imagery to assist in the act of ejaculation. Indeed, in the fully established state the semen may escape while the organ is in a perfect state of repose, and give to the canal in passing through it a burning and painful sensation, instead of a pleasurable one.

While still in the preceding stage of emissions by night the dream may first be wanting, and then erotic feelings so far be absent as not to awaken the sleeper, or if he is aroused he has the consciousness that the erection is quite feeble or that the emission has perhaps occurred from an almost flaccid penis. Instead of occurring at comparatively infrequent intervals, as in the earlier stages, evidences of pollution are now seen perhaps several times in a week or several nights in succession, and in aggravated cases they may occur two or more times in the same night.

When true spermatorrhœa becomes firmly established, after this period of progressive nightly losses, it may require but slight irritation to determine an ejaculation. At first, as before mentioned, either there is a discharge after defecation or urination, attended with sensations along the canal as the fluid passes, or some psychical or mechanical exciting cause, producing erection at the same time, is instrumental in determining the ejaculation. Contact with the opposite sex, scenes upon the stage or elsewhere which inflame the imagination, desire associated with sexual thoughts, or the sight of the nude female form in art as well as in real life may be sufficient, especially in certain sexual perverts, who count in their number

those in whom the sight of the bare nates of the male is alone required to produce an ejaculatory spasm.

In a more advanced stage of the process either the semen flows away mixed with the urine or more or less continually and in an imperceptible manner, or various causes of a non-sexual order tend to call forth its discharge without the intervention of sexual thoughts or erection, and perhaps without appreciable sensations along the urethral tract to make the subject conscious of its occurrence. In a case now under treatment, so slight a cause as running to catch a car may result in pollution.

Incontinence, in the majority of instances, is nocturnal only, and results in cure by marriage or by treatment. Of the cases which become more chronic and show the symptoms of diurnal loss, a small proportion only reach the state of true spermatorrhœa. The latter must be regarded as of fortunately rare occurrence.

Local symptoms embrace changes in the motor apparatus and in the quality and quantity of the seminal fluid. There is frequently, though by no means uniformly, to be made out a diminution in size of the various organs of the external genital apparatus. The testes may become gradually diminished in volume, the scrotum relaxed and pendulous, and the contained veins enlarged. The penis itself may present a somewhat shrunken appearance, though this is not uniformly the case. On the contrary, one often observes a pronounced degree of incontinence in a person of large and turgid organs. When the pendulous penis is diminished in size, the corpora cavernosa appear hardened and the corpus spongiosum much more rigid and firm than usual. These appearances are neither constant nor characteristic, and have a value only when in association with other features.

The urethra presents more important signs. Here, in the early stages, because of the hyperæmic and ofttimes inflammatory state of the pars prostatica more especially, there is hyperæsthesia, which is translated by a sensation of burning or scalding pain at and after the passage of semen, associated with more or less marked sensations of a disagreeable nature in the region of the perineum. If, as often occurs, the vesiculæ seminales are etiologically involved in the production of pollutions by day or by night, a sensation of weight, burning, and throbbing referred to the rectum may precede a discharge from a distended vesicle. General sexual hyperæsthesia is an accompaniment of inflammation, and priapism is likely to coexist with exaggerated sexual appetite.

In the more chronic stages of vesiculitis the symptoms are more those of urethral inflammation and sexual neurasthenia. Examination per rectum shows the vesicles to be enlarged, hot, and tender.

For this examination to give satisfactory results, either the examining finger should be unusually long or the patient's perineum should be flabby and capable of being pushed well in by the fist as the index is being introduced. The patient should stand, with the legs separated and the body bent forward, in a slightly squatting posture, with the muscles well relaxed. The surgeon's disengaged hand should be employed to make counter-pressure over the hypogastrium.

I mention this because text-books often speak of these examinations as though they were carried out with the utmost ease and brilliancy of result.

To collect whatever may be pressed from the vesicle through the ejaculatory ducts into the prostatic and other portions of the urethra, the patient should pass about half an ounce of urine beforehand to wash out the canal. This should be preserved for comparison. After the manipulation the remaining urine is to be passed in two portions. The first will contain whatever the expression has resulted in, and the second will represent the urine as it exists in the bladder. From these three specimens a rough comparison can be made at once, and subsequent examination will reveal the normal and pathological elements obtained from the seminal vesicles.

The changes which the seminal fluid undergoes in spermatorrhœa will be more readily appreciated if its normal composition and secretion are kept well in mind. A consideration of the physiological characteristics of this fluid will be found in the section on Sterility. When chronic vesiculitis is an element in the case, the manual expression of the reservoir will show at times an admixture of pus, and the spermatozoa will, in consequence of the presence of the latter, manifest little or no vitality. In any case when protracted loss of semen has occurred there will be found decided alterations in the quality and at times in the quantity of the fluid. In a general way, it may be said that the changes consist principally in a diminution in number of the spermatozoa, even to the point of entire disappearance, a decrease in their activity, and a more watery and less opaline fluid medium in which they wriggle about.

Such spermatozoa as are present in advanced cases appear shrunken, malformed, and motionless, or show but little activity in their movements.

When discharges have occurred with great frequency, many immature-appearing spermatozoa will usually be seen in any given microscopic field. The bulk of the fluid in these cases is derived from the accessory glands, and represents the non-fertilizing portion of the semen, which flows under stimulation from the walls of the seminal

vesicles, the glands of the prostate, and those of the whole length of the canal.

General Symptoms.—These are to be divided into two classes: those that manifest themselves as a usual thing just subsequent to the pollution or seminal emission and soon pass off; and those that develop at a more remote period and persist for a greater time. Individuals differ greatly in their symptomatic reaction to the shock and drain of spermatic losses. In one there will be an entire absence of any effect upon the constitution, which can be attributed to this cause; while in another such a degree of frequency of pollution as would scarcely lead us to look for systemic results will be followed by the most pronounced nervous manifestations, irritability, dyspepsia, and, finally, by a condition of neurasthenia.

The symptoms comprised in the first class include headache, especially occipital, tenderness of the scalp, backache, sensations of formication, numbness, flashes of heat and cold, a feeling of lassitude and weakness, especially of the extremities, and a disinclination to indulge in mental effort or study; the powers of observation and retention are less acute; besides this there is often drowsiness in the daytime and in some cases irritability of temper. Memory is defective and common words are often forgotten. In boys at school, lessons are acquired with difficulty or soon forgotten.

The more remote manifestations include certain disturbances of the nervous system, both motor and sensory, and digestive derangements which implicate both the stomach and intestines in their functional activity.

Among the nerve symptoms there is one which stands out prominently and has been mentioned by a number of authors—a peculiar restlessness, which prevents the victim of pronounced spermatorrhœa from remaining quiet in one place for any length of time. There is a constant propelling inclination to walk and a nervous irritability which prevents the patient from sitting long in one position. It is quite possible that many members of the tramp fraternity, who continue to roam from place to place, in spite of muscular fatigue and foot-sore condition, are sufferers from this form of nervous affection, which impels them in spite of other considerations to keep on the move. The defective memory spoken of as one of the earlier manifestations becomes more pronounced in the advanced stages, and to the occasional hesitancy for lack of a word is added a decided stammering in speech.

A condition of pronounced neurasthenia may possess the patient with its varied manifestations. Besides those already spoken of may be mentioned anæsthesia and hyperæsthesia of certain parts; painful

skin areas, especially in the precordial region and scalp; and painful neuralgias in general. To this may succeed grave mental symptoms, threatening if not actually leading to melancholia. There is a disposition to be alone, amounting to an actual distaste for the society of friends and companions. The patient has erroneous impressions that his condition can be read in his face, hence the glance is furtive and the eye seldom meets that of the person with whom he is conversing. The idea may become so fixed in the patient's mind that any one casually encountered can read the secret in his glance that he goes about in a state of constant egotistical misery.

Nervous disorders of a more aggravated and serious nature may supervene, and we find that insanity or some other form of brain or spinal affection, such as epilepsy, tabes, or chorea, succeeds this neuropathic state, provided a predisposition to such disorders exists as shown by the family history.

Of the symptoms referable to the digestive tract which we have mentioned none takes a more prominent place than dyspepsia—or rather, that combination of acid eructations, distress after eating, epigastric cramps, heartburn, etc., which is usually understood by this term. To this must be added constipation, flatulence, and occasional attacks of colic. These conditions existing separately or in combination may be attended with marked emaciation.

Upon the part of the respiratory system we find oppressed and quickened breathing and sighing respiration, while the circulatory organs indicate their involvement, by irregularities of heart action, tachycardias of varying degree and duration, and by the subjective sensations of precordial anxiety and the objective signs of anæmia. Of the special organs the eyes are most likely to show symptoms which may be attributed to spermatorrhœa. Among the disorders habitually noted are sympathetic asthenopia or dimness of vision, muscæ volitantes, mydriasis more or less pronounced, and hemianopsia or dimness of half the visual field. When the ears are implicated ringing and buzzing noises are complained of, and instances of actual deafness have been reported.

Diagnosis.

This can scarcely be made with positive assurance even when a number of the symptoms enumerated are found combined in a given instance. We must have the patient's statements to assist us. I say assist, because one cannot be guided wholly by any views which the patient may hold as to what constitutes abnormal frequency of emission, and what discharges are to be regarded as pathological. The

element of spermatophobia must be eliminated. In the majority of instances the dreaded discharges will be found practically harmless, if not physiological and beneficial. Whether or not they remain harmless depends upon our ability to govern the subject's mental attitude in regard to them.

In determining the question of pathological significance of any given discharge, if it be in the nature of nocturnal incontinence, we must be guided chiefly by the frequency of occurrence and by the constitutional effects, if any, which are produced. A statement recently made that an emission oftener than once in ten days is indicative of a pathological condition requiring treatment will not hold good for all cases. The effect is often of much greater importance than the frequency. If the loss is one habitually occurring in the daytime it may be put down as a distinctly morbid phenomenon, provided spermatozoa are present, especially if they are in considerable number and if the discharges are frequent.

The question now arises whether a fluid discharged with accompanying symptoms referable to irritability of the deep urethra, is of prostatic or testicular origin. To determine this point the microscope must be employed. The gross features of seminal fluid are sufficient for presumptive evidence, but an absolute test is found only in the microscopic discovery of living spermatozoa in sufficient number to make their presence of importance. The prostatic secretion by itself reveals a mass of detritus with scattered mucous corpuscles, epithelial cells, and possibly a few follicular casts. It is a glairy, viscid, and rather thick fluid as given off from distended glands, and if any spermatozoids are present they are apt to appear distorted or motionless, not seeming capable of continued existence in the prostatic secretion which has once become abnormal. The absence of spermatic elements is not of itself sufficient for a positive diagnosis of prostatorrhœa, nor is the presence of a very limited number of spermatozoa sufficient for us to say that the fluid is the product of the testes and seminal vesicles. We may in fact have in any given case a mixed discharge and the diagnosis must be guarded until the history has been investigated and the concomitant symptoms have been duly weighed. This is especially true of those cases in which the same causes have been operative to produce either condition, and when the local symptoms are practically identical in each.

When losses of semen have taken place over protracted periods, the spermatozoa may have gradually disappeared until the vanishing point has been reached. If in such a case the microscope is relied upon solely it might lead to error. There are other signs, however, and, as Ultzmann has pointed out, the so-called spermatic crystals

form quickly in seminal fluid which has ceased to show spermatozoids.

The diagnosis must depend largely upon the history in such cases. Even in the absence of spermatozoa we may safely diagnosticate spermatorrhœa if the history shows that there have been habitual losses of fluid after each micturition as well as after straining in defecation, especially if the more remote history indicates excesses of various kinds and frequent pollutions. Since many of the same mental symptoms are present in both prostatorrhœa and spermatorrhœa, even in the absence of spermatophobia, undue weight must not be attached to the diagnostic aid to be derived from them. Despondency and even melancholy may accompany prostatorrhœa.

Prognosis.

This depends largely upon the age of the patient and the length of time during which the losses have occurred; whether the effect upon the system and especially upon the mind has been pronounced; and whether injury has already been inflicted by the very factors which were active in producing the spermatorrhœa. Thus acute illness may be succeeded for a brief period by a state of seminal incontinence which subsides *pari passu* with the return to health. In the same way, if a local lesion has been discovered to account for the condition and it can be corrected the spermatorrhœa may quickly disappear. Either a slight narrowing of the preputial or urethral meatus, an anterior stricture, tightness of the frenulum, or a phimosis may be the cause of the trouble, and its relief will be followed by a disappearance of the incontinence.

Although the constitution may have been profoundly affected by the onanism or excess which has preceded, even here the prognosis is in the main good, since few instances are of such gravity as to endanger life.

If recent gonorrhœa with its attendant inflammation of the deeper portions of the canal has been the etiological force in operation, the prognosis for a prompt recovery is not so good, since here the causative disease is likely to persist for some time, keeping up the hyperæmic conditions.

In nocturnal emissions the prognosis is favorable if the onanism or other sexual error which has determined their frequency can be checked. Most cases can be brought back to the physiological limit of emissions if proper control can be exercised. In diurnal emissions elements are frequently present which render the outlook less bright. Much here depends upon our ability to get at the true un-

derlying causes and to direct intelligent efforts to their correction. The prognosis is to be modified according as the motor function of ejaculation is in a state of healthy activity or has suffered from paralysis, with atony of the ducts or other parts. The subject's mental condition has a modifying influence upon the prognosis as regards ultimate recovery. If the excesses upon which the incontinence depends are the result of mental defect or of serious nerve derangement, it is probable that the losses will continue unless the nervous disorder is cured. In these cases, too, just as in idiocy and imbecility, the onanistic practices are more than likely to be persisted in. If the family history points to insanity, epilepsy, or grave nervous symptoms, the outlook is not bright. In the incontinence of advanced life there is a natural degeneracy to contend with, which prevents our promising too great results from therapeutic effort. Spermatorrhœa resulting from cerebrospinal or other grave nerve disease offers little chance of being cured or even improved.

Prophylaxis.

Spermatorrhœa is one of the preventable diseases, and hence the rational time to treat it is before it begins. Since, as we have seen, onanism enters almost constantly into the history of these cases, we have here a strong argument in favor of persistent efforts to combat this evil and unmanly habit in all possible ways.

The hesitancy which parents feel about instructing their children in that most important branch which deals with the sexual life and function often arises from a groundless fear that by broaching the subject they may themselves be the means of suggesting a practice to youth still innocent. Such fear is usually, I believe, without foundation. If the habit has been begun, as will probably be the case if the boy is approaching puberty, a frank talk may prevent its being continued to the danger point. If he never has known himself carnally, he will usually heed the words of counsel and refrain when tempted. Parents occasionally consult me as to the advisability of talking to their children upon this subject, and I usually advise them to do so when the children are of an age to understand. If once the father secures the son's confidence and talks to him with kindly frankness, good results will follow. A difficulty often encountered is the gross ignorance of the whole matter upon the parents' part, so that success is by no means assured. If the medical adviser is called upon to act the tutor's part, let him remember not to treat his pupil as an unregenerate wretch, but as the boy who is father to the man and as a possible author of his own spermatorrhœa, unless he re-

ceive proper instruction and be directed in a proper course. The sexual ignorance which exists to-day is a reproach to the medical profession, and the increase in contrary sexual instinct depends largely upon the unchecked practices which have been permitted to flourish through ignorance. As I have elsewhere explained, this branch of knowledge cannot well be taught in the public schools, but parents can inform themselves and transmit their knowledge in proper ways and at proper times to their sons. It must surely be something akin to false modesty which prevents the mention of organs and functions whose importance in the economy of nature is so vast, especially when ignorance is often so disastrous. Not only may various weak states be brought on by early error, but the whole sexual life of the individual may be so influenced that normal hetero-sexual attractions will suffer a decline, perverted instincts will be engendered, and various sexual neuroses will develop.

In broaching the question with one whose confidence would be secured, everything in the nature of levity or ridicule should be avoided, and the matter should under no circumstances be treated in a trivial or frivolous manner. Straightforward, sympathetic common sense is what is required. By impressive reasoning the boy's mind can usually be led into proper channels. Since it has been shown that mental equilibrium is interfered with more by derangement of the procreative powers than by that of any other function, all precautions should be taken to prevent morbid brooding over real or fancied seminal losses, especially in those whose antecedents render them predisposed more than others to insanity. Parents, teachers, religious instructors, and physicians may rest assured that the boy will acquire a faulty knowledge of those subjects about which they neglect to instruct him in a proper manner from the pernicious literature of the self-seeking quack, which is sure to find its way into his hands. The mailing lists of many of these charlatans are made up largely from the catalogues of boys' schools, and the pamphlets distributed are well calculated to cause the youth to magnify his vague symptoms and perhaps bring on results more to be dreaded than those which would naturally follow his indiscretions. For a parent to grant license to a growing son in the matter of illicit sexual intercourse is incompatible with reason or safety. Besides the danger from infection with loathsome diseases, excesses may be readily fallen into, the results of which equal those from onanism. Continence in no wise interferes with continuance of perfect health, and erroneous views to the contrary should be corrected.

Treatment.

In most cases the treatment must be both local and general, but before starting upon a plan of medication and instrumentation we must search out, as far as it is at all possible, the causes which have been operative in establishing the condition confronting us. In one case it will be the vicious habit which first of all needs correction; in another the excess which must be put in check. At times constitutional defects and derangements must receive our first attention; at others we have but to direct our energies to the correction of local derangements, and the battle is won.

Naturally, the management of nocturnal incontinence differs somewhat from the plan of treatment which we would institute for pollutions occurring while the patient is about his daily occupation, or for that form in which there is true seminal loss after the passage of fæces or urine. In the former case we must see to it that there is nothing in the evening habits which would induce congestion of the parts, and the diet, drinking, and bathing habits must be regulated accordingly. The bed on which the patient lies should be preferably a hair mattress. Some device may be resorted to in order to prevent the dorsal decubitus, since lying flat upon the back favors by mechanical pressure an evacuation of the vesicles. The bladder should be emptied for the same reason, not only upon retiring but also when the patient awakens during the night and in the early morning; or he should arrange to be awakened for this purpose at a stated hour. In a word, the direct exciting cause as well as the more remote underlying constitutional condition must receive our careful consideration.

In one case it will be a phimosis which calls for circumcision before we proceed further in our attempts at cure; in another it will be a strictured state of some portion of the urethra, perhaps of the meatus alone, the correction of which is all that will be found necessary to cure the symptom it has occasioned. In still other instances we shall find one or the other of the many deviations from normal conditions which may excite to seminal loss. Gonorrhœal or other inflammations of the urethra will need to be cured. Seminal vesiculitis, prostatitis, epididymitis, orchitis, or cystitis implicating the neck of the bladder will require treatment. The rectum must not escape our attention. Lesions or pathological conditions here located are frequent sources of irritation which induce ejaculation out of season. The nerves of this whole region, when irritated, as by ascarides, fissures, fistulæ, hemorrhoids, pruritus, or the presence of hardened fæces, act reflexly upon the ejaculatory apparatus. The correction of

whatever is here found to be abnormal may put an end to the incontinence for which treatment is sought.

Through rectal exploration the state of the seminal vesicles is made out, and in the spermatorrhœa of plethora or overdistention of the organs the contents may be pressed out and massage applied by the finger tip. The condition of the prostate is also best appreciated by means of the rectal touch, and this method offers such fruitful results in diagnosis that it should never be neglected.

Conditions of the general system which cause the functional derangement are usually of so serious and firmly established a nature that they rise in importance far above the resulting symptom of incontinence. This purely symptomatic form of seminal loss must naturally be differentiated with care from that which is primary, in deciding upon a line of treatment. In diurnal losses we must search for local lesions of the deeper urethra and adjacent parts, as well as for affections of the nerves which preside over ejaculation. The centres governing this act are situated, as we have seen, near the centres for vasomotor innervation, and agencies which affect the one are apt to influence the other.

Local Treatment.

This consists chiefly and, as we have seen, at times wholly in correction of the pathological process which is at the root of the functional disorder. It is usually, in the early stages, a hyperæmia of the prostatic portion which must be subdued by calming injections, the careful and methodical passage of smooth, metallic instruments, instillations and hydrotherapeutic procedures, rectal douches, and douchings of the external genitals. The latter I prefer to have carried out only in the morning, when nocturnal pollutions are in question, since at night excitation may be occasioned by determining an increased supply of blood to the parts and thus rather favor emissions than otherwise. In true spermatorrhœa douches may be ordered both night and morning, and salt may be advantageously added to the water for its tonic effect, especially in advanced cases. In the latter when atony is present more energetic measures must be resorted to. Frictions after the douche, alternating hot and cold streams, and alternating hot and cold sitz baths, will be found of benefit. When hyperæsthesia accompanies the congested state *metallic sounds* introduced regularly fulfil the double indication of pressing out the blood for the time being from the distended vessels, and of so blunting the nerve endings that the hypersensitiveness becomes gradually diminished. To effect this object the patient should pre-

sent himself for treatment on alternate days for a season, the intervals being gradually lengthened as improvement goes on, until a period of a week or ten days intervenes between the applications. The length of time which the sound should be left *in situ* varies with the extent of the hyperæsthesia and the relief obtained. Most cases will receive all the benefit that can be secured in this way by a ten-minute contact with the instrument, which may be lubricated either with some bland liquid, such as albolene, liquid vaseline, or phenolated sweet oil, or with a mildly medicated ointment. Various topical remedies have been advised as suitable for introduction in this manner or upon a cupped sound, which is a surer method, or by means of a specially devised instrument for depositing suppositories in the deep urethra, of which we shall presently speak. Very chronic cases may receive greater benefit from a more lengthy contact of the metallic instrument, while on the other hand very acute cases will improve more rapidly from a three- to five-minute contact only. The size of the sound should be gradually increased at each sitting until the full calibre of the canal, as shown by measurement, has been reached. When the meatus does not admit the proper number, it is probable that the incontinence itself will be benefited by a meatotomy.

Among hollow instruments for depositing medicated cones or suppositories in the hyperæsthetic and congested areas of the canal may be mentioned Harrison's so-called pessary catheter, and similar devices introduced by Weltzmann, Dittel, and others. By means of these instruments cones of any desired length and medicated in appropriate strength may be deposited at points accurately located and measured off beforehand. The cone, having a rounded or acorn-shaped extremity facilitating introduction, is pushed from the end of the instrument by means of an obturator or stylet after the tube has been introduced to the point desired.

Among the drugs found useful for employment in this way are ergotin, of which one grain can be used in each cone; fluid extract of gelsemium, ♏ v.; extract of belladonna, gr. ss.; iodoform, gr. i.; thallin, gr. i.; aristol, gr. i.; airol, gr. i. Zinc and other astringents, and morphine, cocaine, or other drugs of a sedative nature may be added to the list, as the requirements of different cases may suggest.

Cauterization is indicated in the more chronic and obstinate examples, especially in those of long standing when the hypersensitiveness has been succeeded by a condition of inertia and lack of tone. The parts being in a relaxed and torpid condition, the stimulating effect of a caustic is required. Lallemand's instrument or Langlebert's modification or other specially devised *porte-caustique* may be

used for this purpose. Here it would not answer to have the suppository containing a strong percentage of silver project from the mouth of the instrument, for there would then be an effect produced upon the whole extent of the urethra. In the Dittel instrument the suppository is introduced at the outer opening and pushed by the obturator the whole length of the instrument, to be deposited at the proper point. One-third grain is the usual quantity of silver in each suppository. The same purpose is effected by means of the Ultzmann deep urethral syringe, with which a few drops of any desired solution of silver may be locally applied. This instrument can also be made use of to bring concentrated solutions of astringent substances into contact with limited areas, a course which in some instances results in decided benefit. Here, too, the cold-water sound or psychrophore of Winternitz will be found of value, giving at the same time the sedative effect of continued cooling and the benefit of pressure. The advantage over the sound is that the latter does not remain long cool after it is brought into contact with the heated and perhaps inflamed tissues. The effect upon the caput gallinaginis can be well regulated by means of this double tube, and when desirable hot water may be substituted for the cold, or they may be used alternately.

Electricity has here, as elsewhere in genito-urinary work, a sphere of utility. I have seen decided benefit result from a course of galvanism; the negative metallic bulb of appropriate size may be introduced into the prostatic portion of the urethra or applied near the mouths of the ejaculatory ducts, while the positive sponge electrode is pressed against the perineum or any indifferent surface of the body. Only mild currents should be used, especially at first, not exceeding five milliampères, and the sittings should extend over a few minutes only. These, however, may be repeated at short intervals—daily or every second day—and as improvement goes on the intervals may be lengthened to from three days to a week. It is probable that in atonic forms, when there is loss of motor power and the ejaculations are feeble, the faradic current may be of advantage, especially in cases showing anæsthesia of the parts and in those in which seminal losses occur with the penis in a flaccid state. Here it has been found that better results are obtained when the negative electrode is applied in that portion of the rectum which corresponds to the prostate, while the anode is placed over the perineum.

General faradization or the application of the galvanic current to the spinal region is of utility, but a consideration of these measures belongs more properly to the following section.

General Treatment.

Here faradization can be combined with drug medication, hydrotherapy, massage, hygiene, and all other measures which will be found at one time or another of benefit in suitable cases. Constipation exists with pronounced frequency in spermatorrhœics, and especially in false spermatorrhœics or those who may be said to suffer from spermatophobia. The hardened fæces, the straining necessary to an evacuation, the pressure through the rectum upon the seminal vesicles, ejaculatory ducts, Cowper's or other glands, prostate, and all the regions involved, act in a mechanical way to press out the various secretions. The constipated condition must therefore be first of all relieved. One of the natural waters, such as Püllna or Hunyadi, or an occasional dose of Epsom or Rochelle salts, is of benefit. While it is not probable that constipation of itself can be the cause of true spermatorrhœa, it may induce emissions in sleep, and when losses by day exist from other cause it tends to aggravate the condition, and hence should always be corrected. Faradization to the abdomen may aid in securing this effect. Prostatitis is frequently present, and must be treated in a general as well as in a local manner, and until it is relieved the reactionary effect upon the natural movements of the bowels is unfavorable.

Hydrotherapy applied in one or the other of its many forms or in a combination of several of them is of great value in all forms of seminal losses. Besides the early morning plunge, the cold bath or sponge, sprays directed against the spinal column, the Scottish douche, the ascending douche against the perineum and external genitals, the dripping sheet, the wet pack, sitz baths, and cold frictions, all have a tonic effect upon the nerves, and by improving digestion, assimilation, and general nutrition indirectly prove markedly beneficial to the more localized affection. A powerful effect can be secured by heating the body in the sweating box before applying the cold douches. Friction of the whole surface, especially with salt water, followed by dry rubbing until the skin is aglow, offers in a most simple manner a plan of treatment applicable to almost all cases and highly beneficial in most of them.

Hygiene, both general and sexual, is of great importance. The daily life should be regular, the diet non-stimulating, the mind free, and the bowels active. Alcohol should be forbidden, especially at night. All that tends to engorge the prostate should be studiously avoided. Out-of-door exercises should aid in keeping the mind engaged and free from suggestive thoughts, since the lascivious dreams

of night are often but a reflection of the thoughts by day and may be active agencies in seminal emissions.

Copulation is in most instances detrimental to the patient and instrumental in delaying the cure. In certain cases, however, marriage is followed by the most beneficial results, and if it occurs in the natural course of events and is not entered upon with the sole view of finding in it a cure, well and good; but it should never be urged nor even advised as a therapeutic measure.

Bicycle exercise as well as horseback riding is to be advised, especially in instances showing engorgement of the hemorrhoidal veins. Wherever there is enlargement of an organ, be it prostate or seminal vesicle, without inflammation, I believe that carefully regulated exercise on the wheel, with a proper fitting and properly adjusted saddle, will result in improvement of the condition. Even riding over uneven pavements might be advised, to give, as it were, a vibratory massage to the perineum and organs situated within the pelvis.

Remedial agents of a more strictly medicinal nature are numerous enough, but those that are truly effective are few indeed. In order to choose the proper drug and use it intelligently, the exact condition to be relieved must be kept constantly in view. Tonics are much too apt to be taken where sedatives are in reality required, and the patient doses himself in a haphazard sort of a way, without securing the hoped-for benefit. Among the most useful drugs for sedative effect are opium, camphor, and hyoscyamus. The bromides exert an especially beneficial action upon the abnormal excitability of the genital centre. The monobromate of camphor is notably efficacious in some cases. In the spermatorrhœa of plethora, Bartholow recommends a combination of bromide of potassium and digitalis. Belladonna and gelsemium are also highly spoken of as efficient remedies.

It is in the later stages and in the atonic forms that strychnine, quinine, iron, phosphorus, and drugs of similar tonic effect have their field of greatest usefulness. They may be administered separately or several may be given in combination. A very useful admixture is that of phosphorus with strychnine and iron, or the phosphorus may be used in the form of phosphide of zinc. The drug which has of late seemed to me to give the best result is the ammoniated sulphate of copper. I have certainly had numerous successes with it in incontinence of urine as well as in seminal incontinence. It is a powerful nerve tonic and was recommended [26] originally for incontinence of urine, after it had proven itself especially effective in nocturnal pollutions. Of the following mixture five or six drops may be given in water, morning and night:

℞ Cupri sulphat. ammoniat., ... gr. vi.
Liquoris ammoniæ, ... gtt. x.
Aquæ destillat., ... ad ℥ i.

Where no organic process is in question, too frequent nightly emissions should soon cease under the use of this drug alone, or when its administration is combined with hygienic regulations or perhaps some of the other means of cure which we have enumerated.

Sterility.

Looking upon sterility of the male, as we do at the present day, in the light of modern advance, it is unquestionable that gross injustice has been done the opposite sex in times past. The legal status of the woman who was a party to a childless marriage has been far from enviable in many countries and at many periods of the world's history. Even to-day among the orthodox Jews the husband may divorce the wife who has remained seven years childless.

It is more than probable that laws made by man to govern the case were framed more in ignorance than in egotism. If the woman did not conceive it was naturally thought to be because of some fault or defect upon her own part, and the discovery of any diseased condition of the pelvic organs only served to confirm the opinion formed. Presumably then, as now, gonorrhœal salpingitis and other affections of the adnexa prevailed and resulted in many fruitless unions, for which the male was primarily to blame, to say nothing of those instances of sterility affecting the male partner alone, but for which the female received censure.

Even to-day, it is the woman who instinctively, as it were, seeks in her own person the cause of non-fructification and presents herself to the physician to discover why it is that she does not become pregnant, and to demand relief from her supposed defect. We are only beginning to realize how much blame, both direct and indirect, must attach to the male, when normal sexual union fails to result in impregnation. Vedder,[9] of Christiania, in three hundred and ten instances of sterility in marriage, found that seventy per cent. were due to the husband, either through azoöspermia or impotence, or because of the wife's infection with gonorrhœal disease from her male partner. This casting of blame upon the woman in only thirty per cent. of the cases is in striking contrast to the percentage as given by most authors. One recent writer[33] says that "few would subscribe to the opinion promulgated by the late Dr. Gross that in more than sixteen per cent. of sterile marriages the fault is to be ascribed to the man and not to the woman."

Definition.—Sterility as it concerns us at the present time may be

defined as the inability upon the part of the male to procreate his species. It is usually an accompaniment of impotence, but *impotentia generandi* may exist without loss of power to perform coitus.

Etiology

The causes of sterility must be divided into those which have to do with the spermatozoa themselves; those which concern the passages through which the sperma passes or the motor apparatus which is active in the propulsion of the fluid; and those causes which are psychical, either of embryonic origin or acquired. In the first class, the sexual organs may be in all respects well formed and so far as appearances are concerned normal in functional activities.

An etiological classification has been suggested in which sterility is to be looked upon as *organic* when there is obstructive derangement on the part of the ejaculatory apparatus; as *atonic* when it results from a condition of inexcitability of the ejaculatory centre; as *anæsthetic* when due to a lack of sensitiveness in the nerve filaments of the glans penis; and as *psychic* when the mental activity is sufficient to inhibit the genital centre in the spinal cord. Before proceeding to a study of the pathological changes which render the semen incapable of performing its normal generative function, we must first review the physiological properties of the impregnating fluid.

Normal Composition and Secretion of Semen.

The seminal fluid cannot be considered as constituted wholly by the secretion of the testes alone. It is rather a composite product of these organs, together with the normal secretions of those accessory glandular organs which are connected with the urethra. These adnexa include, besides the mucous glands of the urethra itself, Cowper's, those of the prostate, and the secreting surfaces of the seminal vesicles. In the latter receptacles the testicular secretion is stored up for a longer or shorter period, and has ample time to become mixed with the normal secretion of these organs before it is thrown off. In fact, the whole mucous area, over which the semen which is elaborated in the seminiferous tubules passes before it finds its exit at the meatus of the urethra, contributes to its composition. It is a thick, whitish, or opalescent fluid, very suggestive of boiled starch, containing, besides spermatozoa, a variable number of spermatic cells, seminal granules, and squamous and columnar epithelium. The fluid has an alkaline reaction, an odor said to suggest freshly sawed bone or bone marrow, and when recently voided and exposed to the air it coagulates after a short time, but subsequently becomes more fluid than it

was at first. The quantity normally thrown off varies from two to four drachms. If allowed to stand in a test tube about half the bulk deposits after a few hours, representing the solid ingredients, the upper half remaining liquid. In polyspermia, a rare condition, twice the normal quantity of semen may be ejaculated, the increased bulk consisting chiefly of the watery constituents. The spermatozoa alone constitute the fertilizing element of this fluid, and are estimated to exist in man in the proportion of sixty thousand to each cubic millimetre of seminal fluid. The same calculation would give in the neighborhood of two hundred and twenty-five million of these minute elements of life as the number present in each normal ejaculation. If, as is supposed, one of them alone is sufficient for the fertilization of an ovum, it would seem that nature is most lavish in her supply of these particular cell elements. If, furthermore, we believe that each separate cell may contain not only that which goes to reproduce the form and feature, but the very traits of character and disposition of the progenitor as they will be developed in the offspring, then the wonder of the whole matter seems beyond the possibilities of our powers of conception.

The spermatozoid is the product of the testicles alone. In man, and in most of the higher animals as well, its form and action are most suggestive of a minute tadpole. It is the equivalent of a cell whose nucleus is represented by the head, while the cell body is replaced by a delicate layer of protoplasm enveloping the head, and forming the tail. The tail has a continuous lashing or cilia-like motion so long as the spermatozoid is possessed of vitality and finds itself in an alkaline medium suitable for its continued existence and motility, and the general aspect of the microscopic field is one of great animation. Each separate squirming spermatozoon seems endowed with powers of perception and wriggles about as though with definite purpose.

The seminal granules are minute particles, averaging 6 μ in diameter. They take stains deeply and are supposed to be derived from the disintegrated nuclei of the nutritive cells of the seminiferous tubules. According to some scientists,[28] they are eliminated from the spermatozoids in their process of maturation, and correspond to the extrusion globules of the ova.

Some interesting experiments which have recently been carried out upon dogs[27] have a bearing upon our knowledge of the development of spermatozoids and the action under stimulation and repose of the secreting function of the testes and accessory generative glands. It has been found that if the semen is artificially extracted each day, the total quantity not only gradually diminishes, but the number of spermatozoids in each cubic millimetre is likewise markedly de-

creased. This decrease is more pronounced if several ejaculations are produced in the same day. As the result of a short period of repose, there is noted a fourfold increase in the number of spermatozoids, while an eight-day interval of rest results in a smaller number being found than were originally present.

This same observation is to be made clinically in a modified degree. If coitus is frequently repeated the number of spermatozoids diminishes, while after a period of rest they become more numerous. In the same way, after a period of freedom from emissions the size of the individual filament is larger, while if the emissions are frequent they appear smaller, having had less time in which to attain full development.

Normally, each microscopic field should represent in round numbers one hundred spermatic elements. The average size in the monkey is given by St. George[29] as 5μ for the length of head and 50 μ for length of tail. The breadth of head is 3 μ and its greatest thickness 1 μ. In man the measurements are approximately the same. Schweigger-Seidel distinguishes a "middle piece" between the head and the tail, which in man usually measures 6 μ. Kölliker first showed that in spite of the animal-like appearances and motions of the elements, they were not independent living beings, but simply elementary portions of the organism; and Henle agrees with this observer in regarding the head as a metamorphosed nucleus of the spermatic cell, and considers the formation of the tail as depending upon a connection of the head with the cell. Schweigger-Seidel looks upon the filament as a metamorphosed, singly-ciliated cell.

In some fields an occasional element will be noticeable by the relatively excessive size of the head. These occur especially in the stored-up semen of continence. I have called these the "old-father spermatozoa." Other unusual forms are more rarely encountered in the double-headed and double-tailed freaks. Hydrocephalic children and monstrosities with two heads upon a single body or two bodies joined to one head, are strongly suggested to the mind by the appearance of such unusual vital elements. Spermatic crystals form in colorless, transparent rhomboids when normal semen has stood quietly for several days. When no spermatozoa are present to keep the mass in motion and thus interfere with crystallization, they form very early and may thus have a diagnostic significance.

Abnormal Features of Seminal Secretion.

Modifications occur in the semen which cause it to assume pathological peculiarities, in both its quality and its quantity. These deviations from the physiological characteristics which we have re-

viewed may or may not have a bearing upon the fecundating power of the fluid. The entire absence of vitalizing elements in the ejected fluid is the first etiological factor in the study of sterility which will claim our attention.

Azoöspermatism.—In this condition of true idiopathic sterility the power of performing coitus remains unimpaired and ejaculation takes place in a seemingly normal manner, both subjectively and objectively. There is, however, so important an alteration in the ejected fluid that it falls short of its mission of fructifying the ovum. The semen may appear normal both in quantity and quality, so far as the gross appearances are concerned; but if it be subjected to microscopic analysis, its total lack of functional worth becomes at once apparent, in the absence of spermatozoids.

This peculiar condition may be due to causes which are either mechanical or organic. Of the former may be mentioned occlusion of the vasa deferentia, resulting from traumatism, inflammation, or new growth; funiculitis, cryptorchism, etc., although the latter condition more commonly results in sterility for the reason that the testes, retained in the abdomen, remain undeveloped, flabby, and are functionally inadequate to the production of fertilizing spermatozoids.

Of the organic causes, we have those which may be considered as local and others as general. The local would include changes in the testicles, due to epididymitis and orchitis, especially when double; and those due to other local diseases, such as hydrocele or varicocele, or to local injury. The general would embrace those nutritive changes which have resulted from constitutional diseases, such as syphilis, diabetes, tuberculosis, poisoning, chronic alcoholism, excesses in sexual indulgence, including onanism, and injury to the nerve centres, especially to the brain and more particularly the cerebellum.

When the spermatozoids have not entirely disappeared but only occur in diminished quantities, the condition has been called *oligozoöspermatism.* The quality as well as the quantity shows deterioration, and the individual element is small and shrivelled and its movements are either quite sluggish or have ceased entirely. This condition is a frequent accompaniment of bloody semen. The sterility is proportionate to the physical features presented, but it may be considered as absolute when there is no evidence of life noticeable in repeated examinations of the fluid. An entire absence may be noted at one time, and in a subsequent examination, after a period of repose from sexual exertion or freedom from pollutions, an increased quantity may be found.

Hæmatocele furnishes an example of a pathological condition in

which a considerable diminution in the number of spermatozoids occurs. Azoöspermia is in most instances a permanent condition, and furnishes the most frequent cause of childless wedlock. It may occur without the etiological factor of blood or pus.

Another cause for sterility which has to do with the seminal fluid alone is that condition called *aspermatism*, which exists when there is a total deficiency in the production of seminal fluid, or when, having been produced, it is diverted from its natural channels and in the act of ejaculation fails to pass out at the meatus in the natural way. An aspermatic subject may present some organic defect of the genitals, by reason of which the semen is either not produced or is thrown off by some faulty route. Here, as in many of these abnormal states, the sexual desires, libido, powers of erection, intromission, and ejaculation persist in a normal manner, but at the orgasm there is no emission of seminal fluid.

We might classify aspermatism according to its dependence upon functional disturbance or upon some well-defined pathological lesion. It may present itself as a congenital defect in which there is a state of non-excitability of the reflex centre of ejaculation. A pathological change can in many cases be distinctly made out. Instances are recorded in which at each ejaculation the semen has been forced back into the bladder by reason of a tight stricture or similar obstruction in the calibre of the urethra. There is no deficiency in the secretion of the fluid, but its excretion is mechanically hindered.

The obstruction may exist in that portion of the urethral canal into which the ejaculatory ducts open and may result from operations for stone which have severely injured the region of the verumontanum. It has also been thought that the plan of treatment by cauterization of the prostatic portion of the urethra with the solid stick of nitrate of silver, once so prevalent in Germany and other parts of Europe, has been fruitful in the production of sterility from this same cause. Unquestionably, any decided injury in this portion of the canal, whether it be from burning, bruising, cutting, or disintegration of tissue, such as might follow abscess formation, neoplasms, or infiltrations, may so interfere with the ejaculatory canals themselves or their orifices as to disqualify them for the passage of seminal fluid in the natural direction. At times in perineal section for the relief of calculous disease the ejaculatory ducts are cut across and thus obliterated, or the injury may involve the mouths of the ducts alone. Concretions may form in the seminal vesicles, and in their attempts to pass through the ducts may occlude them, or a sympexion lodging in one duct may, by pressure upon the opposite one, occlude it as well. Reliquet mentions such an instance.

The obstruction may be located much farther back in the generative tract, as when the canal of the epididymis is obliterated. Naturally, we expect this to occur only when a double-sided epididymitis has followed blennorrhagia or syphilis. This is a rule, however, to which exceptions have been pointed out. Sinéty has observed sterility in at least two instances after unilateral epididymitis.[30] It is not quite clear how this can be the case, unless some preexisting disease has interfered with the healthy function of the opposite side or some coexisting structural defect is present. Double funiculitis, obliteration of the vasa deferentia, or occlusion of the common ejaculatory duct may be the cause at fault.

Temporary aspermatism is the name applied to those conditions in which the semen flows at some period of time after the erection has subsided and the organ has again become flaccid, as in emission during sleep shortly after copulation. It is seen for the most part in nervous subjects, and a reflex neurosis may be present. Those cases in which stricture or concretions obstruct the outflow are temporary also, in the sense that operation for removal of the impediment cures the sterility. Here, at the moment of ejaculation, there is often very decided pain.

In seminal vesiculitis and in prostatitis the semen may be mixed with pus in such proportion as to destroy the viability of the vital elements, or, if not actually destroyed, they may be so inhibited in their activity as to become powerless to fecundate.

Gonorrhœa of the seminal vesicles is a condition frequently overlooked, but one which is a fruitful source of infection in those recurrent cases of urethritis which so mysteriously make their appearance in certain subjects after a nocturnal emission as well as following the act of coitus. In this condition, especially when both vesicles are implicated, Lloyd's process of expression of their contents will demonstrate that spermatozoa are diminished in number, restricted in their motility, or are perhaps wholly wanting. In like manner, pus from a prostatic abscess destroys the spermatozoids, while any suppurative inflammation of these parts may result in cicatricial occlusion or stricture of the duct. The normal secretion of the prostate gland is favorable to the continued vitality of the spermatic elements, and, as we have seen, forms a considerable portion of the bulk of the seminal fluid; but the moment the secretions become pathological from the presence of prostatitis or the like, the opposite effect is produced, and they prove inimical to the life of the spermatozoid.

To revert to the seminal vesicle, we find at times a loss of tone in the muscular wall, which permits of the occurrence of a state of overdistention, leading to temporary sterility. In inflammatory affec-

tions of the vesicle, blood may be present in the discharge with or without interfering with the functional activity of the spermatozoa. This condition of hæmospermia is an interesting one, and we will consider it here at some length before proceeding to discuss those disorders leading to aspermatism which belong to the second class, *i.e.*, those which are functional.

Hæmospermatism.—The presence of blood mixed with the semen may under ordinary conditions have no bearing upon sterility, still it may become so pronounced that, in particular ejaculations, blood almost in its purity may replace the semen; and while this state of affairs persists, sterility will be present. At any rate, the condition has a very proper place among the abnormal features of seminal secretion, and deserves consideration here because of the pronounced mental effect which the presence of blood has upon the average patient. In most instances the ill results are limited to those produced upon the patient's mind, and when his fears have been allayed no permanent harm follows.

The color of blood-mixed semen varies from a bright red to a dull rusty hue, and between these extremes we find orange, light brown, dark brown, and a dull or dark red shade, most pronounced at times upon the borders of a dried stain. The color is of importance, as having a bearing upon the time and location of the hemorrhage, since we can judge of its recent or remote occurrence by the brightness or rusty appearance of the blood stain; and its origin is suggested, in a measure at least, by the same feature. The manner of distribution of the staining throughout the mass is likewise of importance from a diagnostic standpoint. If evenly diffused, giving to the entire fluid a uniform tinge, we may justly infer that the hemorrhage originated within the seminal vesicle, probably upon both sides. If one portion of the area which has been stained by the discharged fluid is deeply colored, while another area is but slightly so or not at all, we may draw the conclusion that one vesicle alone is affected. It was formerly believed that bloody semen originated in the testes and epididymis, but it has been quite conclusively shown that such is not the case, at least in the great majority of instances. Most cases are undoubtedly of inflammatory origin, and the nature of the inflammation is usually blennorrhagic.

When bright and seemingly almost pure blood is ejected, it is always a question whether it may not originate from an overcongested prostate; but if it follows repeated copulative acts carried out in quick succession, it is more likely to proceed from a vessel ruptured in the repeated spasmodic contractions to which the vesicle is subjected in its empty state. If, after an interval of some days or weeks,

a pollution or ejaculation *in coitu* shows a uniform rusty semen, the latter substantiates our diagnosis. A mere streaking of otherwise normal-appearing fluid may depend upon an acute or chronic hyperæmia or an inflammatory disease of the vesiculæ seminales, but probably much oftener has its source in an inflamed or congested state of the prostatic urethra. It is comparatively frequent after acute blennorrhagia, and is occasionally seen in the chronic form. This latter condition is not one of true hæmospermia as we understand the term. When the blood stain is added to the semen in the posterior urethra, as Guyon has remarked, the latter is marbled, as it were, with streaks of red, representing the markings the fluid receives in its passage through the deeper portion of the canal. This is not always clearly to be made out. In a very recent case which was under my treatment for a slight gleety discharge, ungratified but prolonged sexual excitement resulted in ejaculation *intra bracas*. The semen was mixed, so far as the patient could judge, with an equal quantity of bright-red blood. This evidently had its origin in an acute, active congestion of the deep urethra, since subsequent emissions showed no staining.

While, as we have seen, bloody semen is of inflammatory origin and often a symptom of spermatocystitis or chronic seminal vesiculitis, still many cases are non-inflammatory, and this latter class has recently been studied by Jamin.[25] When, for a long time, the seminal bladder has been overdistended and perhaps from prolonged continence (a negative sort of sexual excess) becomes filled with a thickened, gelatinous fluid, bearing a resemblance in its small nodular masses to grains of boiled sago, and perhaps containing veritable gritty concretions, the walls lose their natural tone. If, now, any of the causes of pelvic congestion prevail, such as protracted dorsal decubitus during illness (I have seen brown semen in the case of a man who had been suffering for a fortnight with severe seasickness), continued pressure upon the perineum, as in horseback or bicycle exercise, especially when the saddle is an ill-fitting one and the length of time the pressure is maintained is excessive, the small vessels of the seminal bladder become overdistended and tend to rupture. This rupture may take place at any time before or just at the moment of ejaculation. Even after the bladder contents have been wholly drawn off, the distended state of the vessels remaining, it is probable that hemorrhage may take place *in vacuo*. Here much the same conditions prevail as in the sudden drawing-off of the entire contents of an overdistended urinary bladder or pleural cavity filled with fluid. Jamin believes that the theory of intravesicular hemorrhage *in vacuo* is tenable.

Spermatic colic is another source of hæmospermia, according to Légales. The small calculi which pass down from the vesiculæ seminales tear the inner coat of the ejaculatory ducts, occasioning pain and hemorrhage. In this case the semen is tinged with blood in striæ as it passes through the wounded canal.

Excessive coitus and onanism are, as already intimated, among the chief exciting causes of hemorrhage.

The vascularization of the seminal vesicles being the same as that of the prostate, we naturally infer that influences affecting one would likewise affect the other organ. Now, in elderly men vascular changes and degenerations are pronounced in the prostatic region, and comparatively slight causes may produce congestions and hemorrhages. It is, therefore, more than likely that the bicycle may for this class of subjects become an etiological element of decided import. The wheel should be used in great moderation by men over fifty-five years of age, and when any hemorrhage from the genital tract occurs after riding in those of about this age, it should be given up entirely. In younger men it seems to me that this form of exercise may be of decided benefit in some plethoric and non-inflammatory conditions of the pelvic organs, and it may have a prophylactic action in certain of the disorders which we have considered.

Besides the discoloration of the semen which is due to an admixture with blood, there are other rarer chromatic changes which must be mentioned.

Blue semen is a peculiar phenomenon whose occurrence has been signalized by Ultzmann, but concerning the nature and cause of which little has been learned. The blue color is most distinct at the border of a stain upon linen.

Wine-colored semen bears a striking resemblance to hæmospermia, but the color has been attributed to the presence of indigo. The microscope suffices for differential diagnosis by the beautiful scales which it discloses. In the fresh specimen the color is grayish-violet, becoming deep red on drying. The subjects are usually of a nervous temperament.

Green semen is the result of the wine-colored semen just mentioned becoming mixed with pus, and this fact renders it the most important of the discolored seminal fluids, so far as their bearing upon sterility is concerned, since we know that all pus in semen is hostile to the functional activity of its vital element. This statement applies equally to all semen having a greenish hue, for this is always indicative of the presence of pus mixed with semen perhaps in other respects quite normal. This combination, however, more frequently produces a fluid having a yellowish tinge. This color verges upon

the green, as Terillon has found, when double epididymitis is present.

The peculiarities in the distribution of the stain upon linen, etc., which we mentioned as furnishing aid in our decision as to the source of the blood in hæmospermia, apply equally in stainings from pus-containing semen. Ultzmann maintained that if the stains were unevenly distributed the neck of the bladder was the probable source, while if the admixture had occurred in the seminal vesicle the stain would be even in distribution. Indigo staining is not incompatible with an abundance of healthy spermatozoa. In some cases of jaundice the semen takes part in the general staining.

Functional Aspermatism.—In the second class, or aspermatism due to functional disturbance we find certain psychical causes at work, and at the time at which a normal ejaculation should take place an inhibitory action is set in motion which wholly restrains the function. In such a state of nervous disorder the patient is prone to lose confidence in himself and his powers, and a condition of psychical impotence is added to the functional sterility. Neurasthenia, debilitating and wasting diseases, and faulty innervation are among the constitutional causes of functional aspermatism.

When the semen becomes much reduced in quantity, the condition is termed *oligospermatism*, which in elderly men is a natural result of advancing years. The spermatozoa are present in exceedingly small numbers, and not infrequently, especially after a double-sided epididymitis, they wholly disappear in consequence of occlusion of the seminal ducts, in which case the term *oligozoöspermatism* is applied. The two conditions are frequently associated, the decrease both in fluid bulk and in testicular quota of spermatozoa depending upon a common cause. Oligospermia may, however, exist alone as an inherent weakness, debilitated state, or inherited lack of sexual development of congenital origin. If in a fresh specimen the elements are seen with spirally twisted, hook-shaped, or curved tails, it is an indication that they were lifeless before expulsion. Sterility may be diagnosticated if all the filaments are motionless, and when but few are moving in a feeble manner its existence is highly probable.

Eunuchism.

Among the causes of sterility which depend upon deficiency in the genital tract and passages, none is more positive and more permanent than this. Sterility is the natural condition of eunuchs, whether they have been deprived of the testes alone and thus transformed into anorchids, or have had the penis removed as well, which, according to Lortet,[31] is the usual custom in Egypt, the procedure consisting in cut-

ting off the penis and scrotum with one sweep of a razor, as close as possible to the pubic region. In one method the penis and scrotal contents are encircled with a tightly drawn thong or band before amputation. No great pains would seem to be taken to check hemorrhage nor to prevent retraction. According to Ebden, an application consisting of peepul tree bark, reduced to a fine pulpy state and mixed with oil, is made over the region, and the patient is retained in a fixed supine position for a week or longer, with earthen pots attached to the feet to prevent movement of the limbs. According to other writers, a mixture of cow dung, rice, and clay is applied in a thick mass, to arrest bleeding and induce healing. According to Lortet, boys castrated in Egypt are buried nearly up to the neck in fine, dry sand, which contributes to the arrest of hemorrhage. After four or five days the subject is disinterred and several layers of cloths soaked in oil are applied over the wound. By another method the cords and root of the penis are torn through by encircling them with a fine but very strong ligature, and drawing forcibly upon the extremities. The child's suffering is intense in this mutilating torture, but hemorrhage is less likely to occur. After operation by this method the parts are simply dressed in the barks of acacias rich in tannin.

As to the results, accurate and authentic data are most difficult to obtain, and authors differ widely in their statements concerning the mortality. Lortet believes that in whatever manner the operation is performed, two-thirds of the children succumb, while Bow has been informed that in Hindoo castration a fatal case rarely if ever occurs. Hayman [32] considers the operation itself, especially in infancy, not more dangerous than an ordinary amputation. Burckhardt says the operation is fatal in about two per cent. only.

The truth would seem to be, judging of the matter from the standpoint of modern surgery and from the instances which fall under our observation of self-mutilations in the insane, that most cases properly treated should withstand the ordeal, but that no standard can be established for the crude and barbarous methods practised in many places. Undoubtedly the mortality is often very great.

The practice of eunuch-making has existed from time out of mind in Eastern countries, and we know from biblical accounts that its subjects have been at times persons of great distinction and authority. A faulty impression has prevailed that the operation is followed by stunted growth, loss of courage, effeminacy, and invariably by change of voice. Such would appear not to be the case, to judge from the accounts of those who have lived in countries where the practice largely prevails. Little has been written upon the subject, but the reports of travellers and resident physicians lead to the belief

that while some develop a rotundity of body from hyperaccumulation of fat, many others remain lean and lank. Those castrated at the age of seven to ten years remain much as other boys until they reach puberty, when they begin to grow very rapidly and in many instances become noticeable from their height. The lower extremities would seem to develop more than the upper, in much the same way that a capon's legs enlarge while the wings remain the same as those of the unaltered rooster. The change of voice is not an invariable accompaniment, and it would seem to be rather the exception than the rule to find a pronounced development of those feminine traits which are supposed to result from the unsexing process. Many eunuchs do acquire a taste for womanly dress and occupation, and a certain proportion develop sexual instincts of a perverse nature and give themselves up to the practice of pæderastic vices.

It is interesting in this connection to recall the fact that in a certain proportion of the instances of contrary or homosexual instinct in men, we find a lack of development on the part of the genitals, and even when this is not the case we are forced to assume in many instances that there must be a perverted development of embryonic origin to account for the psychical hermaphroditism of which these unfortunates are possessed.

Diagnosis.

The diagnosis of sterility, except in aspermatism, is a matter which the microscope alone can determine with positiveness. The entire absence of spermic filaments at a given time or in a single examination must not, however, be accepted as evidence of a permanent sterile state. Many cases fall under the designation of temporary sterility and many more are susceptible of cure.

Prognosis.

This varies with the etiological factors in a given case, the age of the subject, and our ability to remove the mechanical or cure the pathological conditions upon which the sterility has been found to depend. In most instances it may be said to be unfavorable. As a general rule, those cases which depend upon syphilitic indurations of the epididymides and testes offer a much more favorable prognosis for restoration of function than those which have resulted from blennorrhagic occlusion.

When spermatozoa have disappeared as the result of early and persistent onanism or by reason of venereal excesses, the outlook for

ultimate recovery is bright if the subject can be brought under suitable control and proper hygienic influences can be applied.

Treatment.

The more inaccessible the anatomical structures in which the obstruction is located, the less likely are we to succeed with any plans of local treatment; while, on the other hand, the relief of a urethral stricture may bring about prompt recovery from a condition of aspermatism.[14] The occlusion may be located, though rarely so, to be sure, at the very extremity of the penis, by reason of a tight phimosis impeding the escape of the impregnating fluid. Here functional integrity may be readily restored by operation. Occlusion upon both sides from double epididymitis, fibrous indurations left in the tail of the epididymis after blennorrhagia, and syphilitic deposits in the testes, epididymis, or its canal, may, and the latter indeed always do, require general constitutional measures along with the local treatment. The latter consists in the use of absorbent lotions or ointments, baths, electricity, and massage. In the see-saw blennorrhagic epididymitis which occludes first one side and then the other, there is usually an incomplete shutting-off of semen, which, however, may at a given moment result in loss of fecundity. Here it has been claimed that faradization applied over the testes may so stimulate them to increased activity that the force of the seminal flow itself will be sufficient to overcome the obstruction. It would seem, however, quite as reasonable to suppose that the electricity may have its chief action in effecting resolution in the obstructing deposit. If total occlusion has existed upon both sides from the latter cause for a long time, this or any other form of treatment offers little chance of success.

Prophylactic treatment consists in persistently treating cases of double epididymitis in a most vigorous manner and keeping up medication, if the patient can be prevailed upon to submit to it, until resolution has occurred.

When the testes are atrophic, unless too far advanced, much may be hoped for from a thorough course of galvanism. If, however, complete aspermia has existed for some time, no hope should be held out to the patient that electricity, or anything else for that matter, will alter his unfortunate condition.

In cryptorchismus, likewise, there is little hope that the resulting sterility will improve from any of our efforts. As has been already stated, the testes retained within the abdominal cavity have habitually lost their fecundating power, and no power at our command can supply it to them again.

Syphilis of the testis and epididymis frequently results in sterility, and this would seem at times a fortunate occurrence. It is, however, a form most amenable to treatment. The indication is to administer one or a combination of the iodides in rapidly increasing dose, until the daily quantity consumed reaches or exceeds several drachms, or until resolution has taken place.

When sterility is occasioned by the admixture of pus with the semen, treatment is naturally to be directed to the source of suppuration, whether this be located in the prostatic region, within the seminal vesicle, or elsewhere. Much can surely be accomplished in the chronic form of seminal vesiculitis when the vesicle is distended, atonic, and pouring out in an intermittent manner spermatozoa-destroying pus. Here repeated emptying of the reservoir by digital manipulation, as described in a previous section, the index finger being introduced into the rectum, results after a time in benefit. The manipulation is attended with no inconsiderable difficulty, especially in obese subjects, and even with a long finger practice is necessary to enable one to press out even partially the bladder contents. Massage applied in the same way by the finger tip to a chronically enlarged prostate, which contains within its substance numerous foci of purulent secretion, is a measure which may be most advantageously employed.

In hæmatospermia, Ultzmann advises the instillation of from six to ten minims of a five-per-cent. silver solution into the posterior urethra.

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THE

CHEMICAL AND MICROSCOPICAL EXAMINATION OF THE URINE.

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THE CHEMICAL AND MICROSCOPICAL EXAMINATION OF THE URINE.

HISTORICAL NOTE.

Ocular inspection of the urine as a means of diagnosticating disease was practised in the earliest times of which we have any account. Hippocrates recognized variations in the quantity, color, and translucency of the urine, and many differences in the character of its sediment; he further observed that variations in food and drink were capable of producing changes in the appearance of the urine. The school of Asclepiades attached much importance to the urine as a secretion, but failed to develop anything new in regard to it. Galen did no more than to systematize the writings of Hippocrates. Avicenna, in the eleventh century, observed that fasting, fatigue, and strong emotions produced marked effects on the character of the urine, and that the administration of certain medicines produced changes in its color. Little or nothing more was contributed by the Arabian school. In the twelfth century, however, the study of the urine became so popular that many of the Eastern courts had their official examiners of the urine, and in the thirteenth century Johannes (Actuarius) compiled a work of seven volumes on the urine in which probably everything extant of knowledge or speculation about this secretion was given in the fullest detail. Gilles de Corbeil (Ægidius Corboliensis), court physician to Philip II. of France, wrote a Latin hexameter poem on the urine. Following this, there was a gradually growing reversal of opinion, and inspection of the urine fell more and more into disrepute until it became the subject of ridicule, as may be seen on the canvasses of the genre painters of Holland in the early part of the seventeenth century, and in the plays of Molière, who never lost an opportunity to ridicule the physicians of his time. Nevertheless, towards the close of the century, we find Van Helmont and Boerhaave giving to the urine that careful study which laid the foundation for future scientific research.

With the awakening of the study of chemistry in the eighteenth century, we find the first investigations of the urine which possess sci-

entific value. Cruikshank, Vauquelin, and Fourcroy were among the first to engage in this branch of the study. Bellini, of Florence, by evaporating the urine and redissolving the product, demonstrated that the color depends largely upon the degree of concentration. The anatomist, Willis, discovered diabetic sugar. Brandt discovered phosphorus in 1669, but it remained for Margraf, eighty-eight years later, to recognize the fact that it was derived from the phosphates. Rouelle discovered urea in human urine, calcium carbonate and hippuric acid in that of the herbivora. Cruikshank revealed the nitric-acid compounds, calcium, and uric acid. To Cotugno, in 1770, is given the credit of having discovered pus in the urine, although Hippocrates speaks of both pus and blood in the urine as a result of ulceration of the bladder and kidneys. But the discovery which did most to establish a fixed practice of urinary study was that of Richard Bright, who demonstrated the relation of albuminuria to disease of the kidneys, his publications appearing from 1827 to 1831. Berzelius was one of the first in the present century to produce a reliable work on urinary analysis, but valuable contributions soon followed from Lehmann, Becquerel, Liebig, Heintz, and many others. During the succeeding years directions for the separation of the various normal and abnormal ingredients of the urine and the methods of their detection have appeared in rapid succession until the literature of the subject has grown to enormous proportions; it is larger, in fact, than that of any other branch of organic chemistry. The names of many of the investigators are perpetuated in the terms applied to the methods of examination which they devised.

The value of frequent examinations of the urine during disease has never until recently been fully appreciated. This lack of recognition was due in a great measure to the uncertainty formerly pertaining to many of the methods of examination, much of which has of late been overcome. Many substances, the confounding of which led to error or uncertainty in the results of analysis, can now be isolated with comparative ease and certainty. The recent development of bacteriological chemistry has opened an entirely new and exceedingly valuable field in urinary analysis. Not a little advance has been made of late also in the application of the results of urinary analysis to diagnosis, prognosis, and treatment. It is possible in many general affections to determine, from an estimate of the waste and toxic substances eliminated from day to day, the gravity of the disease, and consequently the choice of therapeutic measures best suited to the exigencies of the case.

NORMAL URINE.

The Secretion of Urine.

The purpose of the urinary secretion is the elimination from the system of the products of tissue metabolism and other effete or deleterious matter, and not, as is that of most other organs, the formation of a fluid to be used in the vital processes of the economy. It is not strange, therefore, that the method of its secretion is different and somewhat more complex than that of the other fluids of the body. Modern investigations have failed to overthrow the theory advanced by Bowman, in 1842, regarding the secretion of the urine. They have on the contrary confirmed and amplified it. The secreting portion of the kidney consists of two parts, so different in structure as to render improbable an identity of function. There is, on the one hand, the glomerulus, consisting of a tuft of blood capillaries enclosed in a capsule lined with flattened epithelium which is reflected over the glomerulus, and, on the other hand, tubules lined with glandular epithelium, similar to that of the salivary and other secreting glands. The office of the glomerulus is the secretion of the greater part of the water of the urine, and with it "such highly soluble and diffusible salts as preëxist in adequate quantity in the blood" (Foster). The process involved in this secretion is probably to a great extent one of filtration, as Bowman supposed, but a number of facts seems to indicate that the film of epithelium reflected over the glomerulus exerts some control or power of selection over the substances which pass out of the vessels with the water. In the first place, urea, which is one of the most diffusible ingredients found in the urine, appears to be secreted entirely by the epithelium of the tubules, being forbidden passage through the glomerulus. In the next place, serum albumin is found in exceedingly small quantities, if at all, in normal urine; but if egg albumin, having about the same diffusibility as serum albumin, be injected into the blood, it rapidly appears in the urine. And again, if the integrity of the glomerular epithelium be disturbed experimentally or by disease, serum albumin and globulin are permitted to escape, and even then these two substances do not always appear in the same relative proportions as those in which they exist in the blood. It is also apparent that this secretion is closely under the control of the vasomotor system of nerves, and yet there is abundant evidence that it is not regulated entirely by differences in blood-pressure. An increase of blood-pressure amounting to from one-third to one-half increases the flow

of urine from four to more than twenty fold, providing the velocity of the blood current be correspondingly increased; but interference with the escape of venous blood from the kidney, although increasing the pressure, diminishes the quantity of urine. The rapidity of the blood current is, therefore, no less important than the maintenance of a high blood-pressure.

The function of the epithelium lining the tubules is clearly one of secretion. By it certain elements are withdrawn from the blood and deposited in the tubules. It is the avenue, for example, of the elimination of urea. This is best demonstrated by experiments on amphibia, animals having a double blood supply to the kidneys. The interesting experiments of Heidenhain have proved also, not only that certain substances are removed from the blood by this epithelium, but that in all probability the epithelium of only certain parts of the tubules performs the office of secretion, a supposition which agrees also with the microscopic appearance of the cells. Heidenhain found, for instance, that when sodium sulphindigotate in moderately concentrated solution is injected into the blood of an animal, it is rapidly eliminated by the kidney, leaving its stain only in the epithelium of the tubules. By repeating the experiment upon an animal whose flow of urine has been arrested by a division of the spinal cord, he found that in a short time the coloring matter had passed through the epithelium into the channel of the tubule, staining almost exclusively the epithelium of the first and second convolutions, the zigzag tubules and the ascending limb of the loops of Henle. In the instance of this coloring matter, and in the elimination of urea the epithelial cells probably do nothing more than pick up the substances and convey them from the blood to the cavity of the tubule. In the secretion of many other substances, however, the work of the epithelium is apparently not limited to this. It is believed, for instance, that hippuric acid and some of the coloring matters of the urine, which do not normally exist in the blood, are formed by a metamorphosis of other substances in this tubular epithelium. From these facts and others, all of which are fully discussed in the works on physiology, it is believed that the solids contained in the urine are eliminated chiefly by the epithelium of the tubules.

It is probably a fact of much importance that the delicate structures composing the kidney are surrounded by a fibrous capsule, delicate in structure but capable of exerting much resistance, the parenchyma being also separated into numerous small sections by a similar tissue. Reginald Harrison, reasoning from analogy, believes that the power of resistance exerted by this fibrous structure against

sudden expansive force exerted from within, as by acute renal congestion, is an important element in maintaining the abnormal state which induces albuminuria.

Collection of the Urine for Analysis.

Correct results can be obtained from analysis only when the specimen is taken from a mixture of all the urine voided in twenty-four hours. The urine should be collected in a clean vessel with a closely fitting cover, preferably a large bottle, and kept in a cool place. When it is not practicable to obtain mixed urine, the sample should be taken about three hours after a meal, since at this time such ingredients as albumin and sugar are most likely to be present, and they may be entirely absent from the morning urine, even when they are abundant after a meal. Too much importance is not to be attached to the result of a single examination, even when negative.

For microscopical examination the specimen should be fresh, as concentrated as possible, and the examination should be made before alkaline fermentation has set in, since such morphological elements as epithelium and casts are dissolved by alkalies. The addition to the specimen of a little formalin or alcohol, a few grains of chloral hydrate, salicylic acid, or chloroform water assists in the preservation of the urine for microscopic examination.

If urine be permitted to stand in a room of ordinary temperature it so rapidly changes in appearance and reaction that, in from two to three days, it has lost its translucency and its acidity has given place to an alkaline reaction. The loss of translucency is due at first to the precipitation of uric acid and urates; later it may be due to the development of bacteria; and to the action of the bacteria is due the change of reaction, since they break up the urea into ammonia and carbonic acid.

It sometimes happens that the urine becomes more highly acid on standing, the color at the same time becoming darker. This so-called "acid fermentation" is explained by Scherer as due to the action of mucin as a ferment which results in the formation of acetic and lactic acids.

Physical Properties.

Color.

Normal urine has a pale yellow or an amber color, but it may vary temporarily from almost the colorless translucency of water to

a reddish brown; pronounced deviations from an amber hue are not usually permanent in health. High color, as a rule, denotes concentration, the presence of a relatively great amount of solids and coloring matter. This may arise from an increase of the solid ingredients or from a diminution of the water, from the ingestion of a full meal, abstinence from fluids, activity of the cutaneous secretion, or from muscular exercise. It is the urine of warm weather. High-colored urine is usually acid in reaction and of high specific gravity. Pale urine, on the other hand, is of low specific gravity, may be neutral or alkaline in reaction, and contains a relatively small amount of solids and coloring matter. It often results from the drinking of a large quantity of water or from nervous excitation.

The color of the urine varies in disease over a much wider range than in health. It may be either diminished or increased, the change being due either to a relative diminution or increase of the normal pigments or to the presence of some abnormal coloring matter. The color is diminished in the polyuria of diabetes, hysteria and other states of nervous excitement, in renal diseases which increase the quantity of water or diminish the amount of solids in the urine, as sclerosis and amyloid diseases of the kidney and hydronephrosis, and in some cases of cardiac hypertrophy; and it may result from the administration of certain medicines, notably those which exert a diuretic action.

The coloring matter becomes increased for the most part as a result of concentration of the urine, or owing to the presence of such abnormal coloring matter as uroerythrin. A depth of color approaching red occurs in febrile affections, in diarrhœal diseases, in intestinal obstruction, and in conditions which cause hyperæmia of the kidneys, as in cirrhosis of the liver or valvular lesions of the heart. A red color is due most frequently to the presence of blood, but it is sometimes produced by the presence of an abnormal pigment. Brownish tints are produced by methæmoglobin; in multiple melanotic sarcoma the urine frequently becomes almost black, the color deepening as the urine becomes cold. The urine assumes a pale green color in diabetes, when the quantity of sugar is great, and has a dull green color in jaundice, owing to the presence of biliverdin. It frequently acquires a cloudy blue tint in cholera and typhus, from the presence of indigo. Many drugs have the property of altering the color of the urine. Santonin always, licorice sometimes causes a distinct yellow color, rhubarb and senna cause a reddish-brown tint, indigo a blue or greenish color, methylene blue a distinct blue color; carbolic acid, naphthalin, hydrochinon, resorcin, and pyrocatechin, in large doses,

a black color, and creosote in large doses sometimes produces a smoky hue, even a greenish brown after toxic doses.

The following table of colors, devised by J. Vogel, is believed to represent definite quantities of coloring matter in 1,000 c.c. of urine. From it the amount of coloring matter present in any given quantity of urine of any shade may be calculated.

VOGEL'S TABLE OF COLORS.

I.	II.	III.	IV.	V.	VI.	VII.	VIII.	IX.	
1	2	4	8	16	32	64	128	256	Pale yellow, = I.
	1	2	4	8	16	32	64	128	Light yellow, = II.
		1	2	4	8	16	32	64	Yellow, = III.
			1	2	4	8	16	32	Reddish yellow, = IV.
				1	2	4	8	16	Yellowish red, = V.
					1	2	4	8	Red, = VI.
						1	2	4	Brownish red, = VII.
							1	2	Reddish brown, = VIII.
								1	Brownish black = IX.

The amount of coloring matter in 1,000 c.c. of pale yellow urine is taken as the standard of comparison. If, therefore, one volume of pale yellow urine contains one part of coloring matter, an equal volume of light yellow urine will contain two parts of coloring matter, an equal volume of yellow urine four parts, of red urine thirty-two parts, and of brownish black two hundred and fifty-six parts. One volume of yellow urine contains as much coloring matter as four volumes of pale yellow, one volume of red, as much as thirty-two volumes of pale yellow or eight volumes of yellow, and so on.

From this table it is also possible to construct a proportion by which to estimate the quantity of coloring matter contained in the urine voided in twenty-four hours. Thus if 1,500 c.c. of yellow urine are voided, the proportion is: $1{,}000 : 4 :: 1{,}500 : x = 6$; or, if 1,200 c.c. of red urine are voided, the amount of coloring matter contained may be determined by the proportion—$1{,}000 : 32 :: 1{,}200 : x = 36.4$. The first proportion indicates that 1,500 c.c. of yellow urine contain six times as much coloring matter as 1,000 c.c. of the standard pale yellow urine; the second that the 1,200 c.c. of red urine contain 36.4 times as much as the standard 1,000 c.c. of pale yellow urine. In applying the table the urine should be filtered and examined by transmitted light in a clear glass vessel of at least three inches diameter.

The following table, slightly modified from that of Halliburton, indicates the most frequent variations of color with their

causes and the pathological states in which they most frequently occur:

Color.	Cause of coloration.	Pathological condition.
Nearly colorless	Dilution or diminution of normal pigment.	Nervous conditions, hydruria, diabetes insipidus, granular kidney.
Dark yellow to brown-red.	Increase of normal, or occurrence of pathological pigments.	Acute febrile diseases, diarrhœa, late hepatic cirrhosis.
Milky	Fat globules	Chlyuria.
	Pus corpuscles	Suppuration, tuberculosis, cancer, etc., in urinary tract.
	Bacteria	
Orange	Excreted drugs	Santonin, chrysophanic acid.
Lake or smoky to reddish or red.	Hæmoglobin, blood, pigments in food (logwood, madder, bilberry), fuchsin.	Hemorrhage or hæmoglobinuria, scarlatina, typhoid fever, malaria, etc., etc.
Brown or brownish black.	Hæmatin, methæmoglobin, melanin, hydrochinon, pyrocatechin, carbolic acid.	Small hemorrhages, methæmoglobinuria, melanotic tumors.
Greenish yellow, greenish brown, approaching black.	Increase of urobilin, bile pigments, creosote in large doses, inhalation of arseniuretted hydrogen.	Jaundice and conditions due to poisoning.
Dirty green or blue.	A dark blue scum on surface with blue deposit, due to an excess of indigo-forming substances. Ingestion of indigo or methylene blue.	Cholera, typhus, seen especially when the urine is putrefying.
Brown yellow to red-brown, becoming blood red on addition of an alkali.	Substances introduced into the system with senna, rhubarb, and chelidonium.	

Translucency.

Normal urine is nearly or quite clear. Upon cooling, however, a delicate cloud of mucin usually subsides to the lower part of the fluid and remains unchanged upon the application of heat or the addition of alkalies or mineral acids; it may become slightly increased by the addition of acetic acid or alcohol. If the urine be allowed to stand in a warm place for two or three days it becomes clouded by the growth of bacteria, to which reference has been made. During this time also, amorphous urates, some uric-acid crystals, and occasionally crystals of calcium oxalate are deposited, and may sometimes be seen as minute sparkling bodies in the mucin cloud.

Urine that is clear when voided may become turbid on the application of heat nearly or quite to boiling, from the presence of increased phosphates or albumin. The cloudiness of the phosphates vanishes upon the addition of an acid, while that of albumin becomes more pronounced. It should be remembered that the addition of a

few drops of strong acetic acid will almost invariably cause a slight turbidity in normal urine, owing probably to a coagulation of nucleo-albumin.

The urine may be turbid when voided, from the presence of precipitated urates, carbonates, phosphates, excessive mucus, pus, blood, chyle, or bacteria. These substances, with the exception of the bacteria, usually settle in a few hours to the bottom of the vessel, where they form a more or less bulky precipitate.

Tests.—If the turbidity disappears on the application of moderate heat, it is due to the presence of urates; but if heat renders it more pronounced, it is due to the earthy phosphates or such albuminous matter as pus or blood.

A few drops of acetic acid should now be added. If the turbidity disappears, it consisted of the earthy phosphates; if it is rendered more pronounced, it depends upon the presence of albumin, pus, or blood. If little or no change is produced by the addition of the acid, the cloudiness probably depends upon the presence of bacteria.

Quantity.

The quantity of urine voided during a period of twenty-four hours in health depends to a considerable extent upon age, sex, temperament, habits, diet, and drink. The average quantity lies between 1,200 and 1,500 c.c. (40 to 50 ounces). Most authors have placed it at 1,500 c.c., but Yvon and Berlioz, from observations of 347 specimens from men and 314 from women, all in health, place the average as low as 1,360 c.c. (46 ounces) for men and 1,100 c.c. (37.2 ounces) for women. The average quantity voided by children has been thus stated by Maximilian Herz: At the age of eight years, 700 c.c. for boys, 600 c.c. for girls; at ten years, 750 c.c. for boys and 700 c.c. for girls; at twelve years, 1,000 c.c. for boys and 800 c.c. for girls.

The secretion of the urine is more rapid during the daytime than at night, the ratio of the quantity of day urine to that of night being usually from 2 : 1 to 4 : 1. In old age, however, and in cachexia, in cardiac and renal affections, and in diabetes the ratio may become changed, the night quantity equalling that of the day, or exceeding it as 2 : 1.

The quantity of urine is increased in diabetes mellitus, diabetes insipidus, in sclerosis and amyloid disease of the kidney, pyelitis, simple cardiac hypertrophy, hysteria, and convulsions. This increase is known as polyuria.

The urine is diminished in acute nephritis, in all conditions causing either active or passive hyperæmia of the kidneys, in all diseases

accompanied by fever, and in such cardiac affections as reduce the force of the heart's action. Diminution amounting to nearly or quite total suppression (anuria) may occur in acute parenchymatous nephritis, in the collapse following hemorrhages, high intestinal obstruction, such internal injuries as rupture of the liver, spleen, bladder, or intestine, or the reflex shock following catheterization or operations upon or through the urethra (urinary fever). Anuria occurs also in the algid state of cholera and yellow fever, in cholera morbus, cholera infantum. Some medicines, including the anæsthetics, chloroform and ether, at times induce suppression of urine in persons whose kidneys are diseased.

Odor.

The odor of urine is peculiar, slightly aromatic, and quite characteristic, although varying considerably in intensity with the concentration. It is attributed to the presence of minute quantities of phenylic, taurylic, damoluric, and damolic acids.

Urine which has stood for several days in a warm atmosphere acquires an ammoniacal odor, from the formation of ammonium carbonate by decomposition of urea, and later becomes putrescent, especially if it contains much organic matter. This ammoniacal or putrescent odor may be present when the urine is voided in catarrhal, tuberculous, or cancerous disease of the bladder, or in destructive lesions of the kidneys. The urine of diabetes often has the odor of acetone; urine containing cystin has at first the odor of sweetbrier, but soon becomes putrid. Many articles of food, as asparagus and garlic, give a characteristic odor to the urine. The same is true of some medicines. The ingestion of turpentine or the inhalation of the oil of rosemary produces an odor of violets; cubebs, copaiva, the oil of sandal, and some other volatile oils communicate their characteristic odors.

Consistence.

Normal urine is of aqueous consistence, dropping and flowing like water. Highly albuminous and diabetic urine may be reduced in consistence, readily frothing when agitated. The presence of much mucus or pus renders the urine, if alkaline, so thickened as to pour with difficulty from the vessel, not separating into drops, or so viscid as to cling to the sides of the vessel. Chylous urine has the consistence of milk or cream. In fibrinuria, complete coagulation may occur.

Reaction.

Normal urine may be said to be always acid in reaction when the test is applied to the entire volume passed in twenty-four hours. The acidity is due to the presence of acid sodium phosphate, the intensity of the reaction varying to a considerable extent with the diet of the individual and the time of day. It is highest during sleep and before meals, or during the first hour of digestion. A relation exists between the acidity of the gastric juice and that of the urine which, as a rule, amounts almost to a parallelism. The greater the quantity of acid produced in the stomach, either from normal secretion or from decomposition of food, but, especially as a result of the fermentation of milk, the greater is the excretion of acid with the urine during digestion. This relation is disturbed, however, when polyuria follows a meal. About an hour after a meal the acidity of the urine becomes markedly diminished, and may continue to decrease for three or four hours (the alkaline tide), the reaction sometimes becoming alkaline. A diet consisting largely of meat renders the urine more acid; other influences which cause increased acidity are prolonged muscular exercise and the ingestion of acids or saccharin. If the lactic or acetic acid fermentation (acid fermentation) takes place, it renders the reaction more highly acid after the urine has stood for a few hours. Quite recently Strasser has announced that hot baths increase the acidity of the urine while cold baths diminish it.

The urine may have an alkaline reaction when voided, owing either to the presence of fixed alkali (sodium or potassium) or of volatile alkali (ammonia). It is often rendered alkaline by an exclusively vegetable diet, by an unnatural loss of gastric juice, as in vomiting, by the administration of alkalies or the salts of vegetable acids, sometimes by the administration of these acids.

Alkalinity of the urine due to a fixed alkali generally signifies merely a highly alkaline state of the blood, that due to a volatile alkali denotes, as a rule, an inflammatory disease of the bladder. The presence of a fixed alkali is indicated by the permanent blue color given to red litmus paper, whereas a volatile alkali gives only an evanescent color, the red color returning to the paper as it becomes dry.

An amphoteric reaction is sometimes observed in which blue litmus paper is turned red and red litmus blue. Huppert explains the phenomenon as due to the presence of acid and neutral phosphates. In one case observed by the writer, however, a volatile alkali was evi-

dently present, for the pale red color given to blue litmus became deeper as the paper dried and the distinctly blue color given to the red litmus paper entirely vanished as it dried.

The litmus pencil is a new and convenient means of carrying the reaction test.

Specific Gravity.

The determination of the specific gravity or density of the urine is of great value, since it indicates the relation that exists between the water and the solid constituents and enables us to calculate with considerable accuracy the rate of tissue waste during a stated period. The specific gravity of the urine, the whole volume of which for twenty-four hours is 1,500 c.c. (fifty ounces), is in health ordinarily about 1.020, but often varies from this at different times of day. These variations depend upon the quantity and the character of the food, the rapidity of tissue metamorphosis, and the activity of the other secretions, particularly that of the skin. The density of the urine is increased by a diet consisting largely of animal food, which increases the nitrogenous waste, by muscular activity, and by copious diaphoresis. The specific gravity is lowered, on the other hand, by fasting, rest, the imbibition of large quantities of fluid, by external cold, and by other influences which render the secretion more copious.

Pathologically the specific gravity varies within a wide range. In acute glomerular nephritis, chronic passive hyperæmia, and in most other conditions attended by a reduction of the volume of urine, the specific gravity is raised, while in the other forms of nephritis, particularly in renal sclerosis, the density is lowered. A persistent low specific gravity, in the presence of normal or diminished quantity, is highly indicative of an inability on the part of the kidneys to excrete the requisite amount of solid matter, and may constitute a prognostication of approaching uræmic disturbance. High specific gravity, 1.030 or over, in the presence of increased quantity is highly indicative of the mellituria of diabetes.

Methods of Determining the Specific Gravity.—The specific gravity of urine can be determined with sufficient accuracy for all practical purposes by the use of the urinometers in vogue; a more accurate result may be obtained from the picnometer, or by actual weighing. The selection of an accurate urinometer is of importance, since many of those on sale err by several degrees. The instrument manufactured by E. R. Squibbs & Sons is probably the best, owing to the peculiar construction of the bulb, the fluting of the tube to prevent the instrument from adhering to the sides, the correction to house temperature (25° C. = 77° F.) instead of the arbitrary 60° F., and the certifying

of existing errors on the case of each instrument. A thermometer is also provided, but its use is rarely necessary, provided the urine be permitted to cool before it is tested. Enough urine must be poured into the tube to allow the instrument to float freely without reaching the bottom. Any froth that may be present should be removed from the surface by a pipette or a piece of filter paper. The instrument is then inserted and gently tapped with the finger tip to insure its finding its true level, care being taken that it does not cling to the side of the tube, and the scale is read from the under side of the sur-

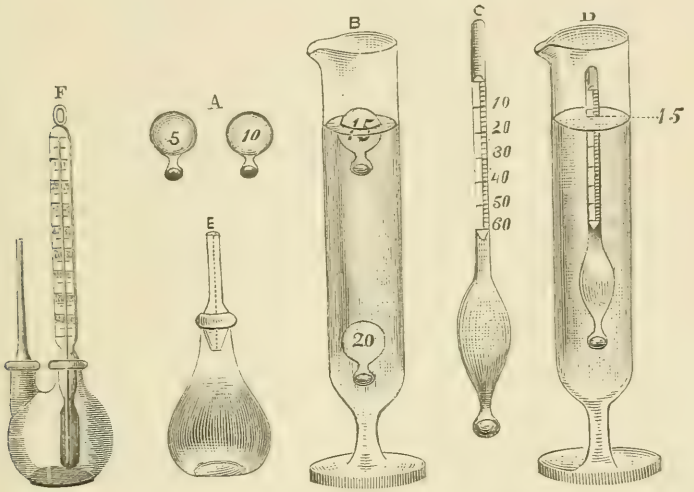

FIG. 44.—Apparatus for Testing Specific Gravity. *A* and *B*, Specific-Gravity Beads; *C* and *D*, Urinometers; *E* and *F*, Picnometers (Tyson).

face, the tube being so held that the true surface, not that of the capillary elevation, is on a level with the eye.

In estimating the specific gravity of freshly voided urine, the thermometer should be used and one degree should be added to the reading of the urinometer scale for every seven degrees of temperature above that to which the instrument has been standardized. If, for example, the temperature of the urine is between 85° F. and 90° F. and the standard of the instrument is 60° F., four degrees should be added to the apparent specific gravity.

Other devices for determining the specific gravity have been introduced. One of the most popular of these, for a time at least, was the use of beads representing the different degrees. The bead which represents the specific gravity of the specimen neither floats nor sinks, but remains wherever placed. An ingenious modification of this method is seen in Dr. Oliver's apparatus, in which a single bead

representing 1.008 is used. If it floats, water is carefully added until it commences to sink, when the level of the fluid represents the specific gravity on a scale on the side of the tube.

When it becomes necessary to determine the specific gravity of a specimen of urine which is too small in quantity to float the urinometer, the urine must be diluted with enough water to make an exact multiple of the original quantity—two, three, or four volumes of water are added. After determining the specific gravity of this mixture, it is only necessary to multiply the last two figures of the result by the number of volumes of fluid used. If, for example, it has been necessary to add four times as much water as urine, and the specific gravity of the mixture is 1.004, the specific gravity of the urine is 1.020. This method should not be used, however, when it can be avoided, as the chances for error are great.

The simplest method of making an approximate estimate of the solid ingredients of the urine is that of multiplying the last two figures of the specific gravity of the mixed urine of twenty-four hours by 2.33, a coëfficient determined by Haeser. This gives us approximately the number of grams of solids contained in each 1,000 c.c. of the urine, from which the total amount may be readily determined.

If, for example, the quantity of urine voided in twenty-four hours had been 1,200 c.c., and the specific gravity is found to be 1.020, the calculation is: $20 \times 2.33 = 46.60$, the number of grams in each 1,000 c.c. The total quantity of solid ingredients is obtained by the equation: $1{,}000 : 46.60 :: 1{,}200 : x = 55.92$ gm. (862.9 grains).

Haines has proposed a modification of Haeser's method which renders the calculation much simpler and fairly accurate. It consists in multiplying the last two figures of the specific gravity by the number of ounces voided in twenty-four hours and the product by 1.1. Thus if the quantity of urine has been 40 ounces in twenty-four hours and the specific gravity is 1.022, the calculation is: $40 \times 22 \times 1.1 = 968$, the number of grains of solids. Since the result of either of these calculations is only approximately correct, their value is limited. The average excretion of solids by a healthy individual of 66 kgm. (145 pounds) weight is 61.14 gm. (945 grains), as calculated by Purdy from the estimates of various authors. Taking this as a standard, therefore, we are able, from the calculation of solids excreted in a given case, to judge of the amount of tissue metabolism that is going on, and this may have an important bearing upon the prognosis and treatment of the case. If, for example, the amount of solids be greatly reduced in a case of nephritis, uræmia threatens. The progress of a febrile or inflammatory disease may be more or less accurately determined from the rapidity of tissue waste.

It must be remembered, however, that the amount of solids present in the urine may be relatively diminished, through faulty elimination, even when the production of waste is greatly increased, as revealed by high temperature.

In health about one-half of the solid ingredients of the urine is urea, but in disease the proportion varies within wide limits; a more accurate method of estimating the quantity of urea should, therefore, be adopted.

Before making deductions from the estimated quantity of solids in the urine allowance must be made for certain variations which experience has shown to result from differences of age, diet, habits of exercise, etc., of the individual. Proportionate increase or reduction must be made from the result to correspond with variations of weight from the standard, 66 kgm. (145 pounds); ten per cent. should be deducted for each ten years of age over thirty (ten per cent. for age from forty to fifty; twenty per cent. from fifty to sixty, etc.). A similar increase or reduction must be made for unusual diet, for rest or exercise, deducting five per cent. for quiet, ten per cent. for absolute rest.

Chemical Properties.

The urine is complex and exceedingly variable in composition. Since it serves as the principal medium for the elimination of not only the waste products of tissue metabolism, but also of many substances which pass through the circulation with but little or no change, its composition varies not only from day to day, but within much shorter limits of time. The chief causes of these variations are the differences in the character and quantity of food taken, the amount of mental and muscular exercise, and to some extent the time of day, the temperature of the air, the age, sex, and temperament of the individual.

Briefly stated, the urine is a solution of certain protein derivatives, as urea and allied substances (uric acid, creatinin, etc.), and of certain inorganic salts, particularly the chlorides of sodium and potassium, always containing other organic substances, one of which gives a reaction attributed by some to mucin, by others to nucleoalbumin. Becquerel found in 1,000 grains of urine 967 grains of water and 33 grains of solids. Of the solids, 24.865 grains were organic, 8.135 inorganic. Hoppe-Seyler's classification gives as the constituents of normal urine the following: 1. Urea and related substances—uric acid, allantoin, oxaluric acid, xanthin, guanin, creatinin, thio-(sulpho-)cyanic acid. 2. Fatty and other non-nitrogenous substances of the series $C_nH_{2n}O_2$—oxalic, lactic, glycerophosphoric acids, very

small amounts of carbohydrates—sugar (Brücke). 3. Aromatic substances—the ethereal sulphates of phenol, cresol, pyrocatechin, indoxyl, skatoxyl, hippuric acid, aromatic oxyacids. 4. Other organic substances—pigments, ferments (especially pepsin), mucin, and humous substances. 5. Inorganic salts—sodium and potassium chlorides, potassium sulphate, sodium, calcium, and magnesium phosphates, silicic acid, ammonium compounds, and calcium carbonate. 6. Gases—oxygen, nitrogen, and carbonic acid. More recent observations have added to this list a lævorotatory body (Haas), animal gum (Landwehr), and the alkaloidal toxins (Bouchard).

The following table gives the average quantity of the more readily determined constituents of the urine excreted in twenty-four hours according to the estimates of Parkes, J. Vogel, and Kerner. The estimates were made according to different methods of observation and analysis. Parkes separates the acids and bases, while Vogel and Kerner calculate only the salts. Kerner's observations were made upon one healthy man, twenty-three years of age, weighing one hundred and fifty pounds, over a period of eight days. The observations of Parkes and of Vogel extended over a larger number of persons and a longer time.

Table of Urinary Constituents Voided in Twenty-Four Hours.

Constituents.	Kerner.			Vogel.	Parkes.		
	Minimum c.c.	Maximum c.c.	Mean c.c.	C.c.	Constituents.	By an average man of 66 kgm. c.c.	Per kilogram of body weight c.c.
Quantity	1,099.00	2,150.00	1.491.00	1,500.00	Water	1,500.000	23.0000
Specific gravity	1.015	1.027	1.021	1,020	Total solids	72.000	1.1000
Water	.....	.....	.....	1,440	Urea	33.180	0.5000
Solids	.....	.....	.....	60.00	Uric acid	0.555	0.0084
Urea	32.00	43.40	38.10	35.00	Hippuric acid	0.400	0.0060
Uric acid	0.69	1.37	0.94	0.75	Creatinin	0.910	0.0140
Sodium chloride	15.00	19.20	16.50	16 5	Pigment and other substances.	10.300	0.1510
Phosphoric acid	3.00	4.07	3.42	3.5			
Sulphuric acid	2.26	2.84	2.48	2.0	Sulphuric acid	2.012	0.0305
Calcium phosphate	0.25	0.51	0.38	.....	Phosphoric acid	3.164	0.0486
Magnesium phosphate	0.67	1.29	0.97	.....	Chlorine	7.—8.120	0.1260
Total earthy phosphates	0.92	1.80	1.35	1.2	Ammonia	0.770	
Ammonia	0.74	1.01	0.83	0.65	Potassium	2.500	
Free acid	1.74	2.20	1.95	3.0	Sodium	11.090	
					Calcium	0.260	
					Magnesium	0.207	

Urea.

Urea, the amide of carbon (carbamide), $CO(NH_2)_2$, constitutes from a third to a half of the entire solid part of the urinary ingredients, but varies in quantity from time to time. It was first separated in an impure state by Rouelle in 1773, and by Fourcroy and Vau-

quelin in 1779. It was first prepared synthetically by Wöhler in 1828, and was therefore the first organic body thus prepared. It crystallizes in clear, silky quadrilateral or six-sided prisms; or, when the crystallization is rapid, as fine white needles. Its melting point is 130° C. (266° F.); it is freely soluble in hot water, in one part of cold water, or in five parts of alcohol, but is insoluble in ether; the aqueous solutions give a neutral reaction. Urea, in crystals or solution, is fairly permanent, but it is readily decomposed on boiling, especially under pressure, by taking up water and splitting into carammonia and bonic acid or into ammonium carbonate, thus:

$$CO(NH_2)_2 + 2H_2O = CO_2 + 2NH_3 + H_2O = (NH_4)_2CO_3.$$

The same change occurs as a result of the action of bacteria in the so-called alkaline fermentation of the urine. Urea has the peculiar property of uniting with acids, bases, and salts.

The liver is the chief source of urea, but other organs probably share in its production; Kaufmann asserts that all tissues of the body produce it. The exact mode of its production is not known, but it is believed to be in part a result of the retrograde metamorphosis of the tissues, including the blood, and in part a result of the splitting up of nitrogenous substances taken into the body as food, all the nitrogen thus entering the body being discharged as urea, except perhaps a small quantity which is eliminated as ammonia by the lungs and skin. Some claim also that a trace of free ammonia is a normal ingredient of the urine.

The average quantity of urea excreted during twenty-four hours is variously estimated as from 20 to 40 gm., the mean quantity by men from twenty to forty years of age being about 33 gm., or, according to Roberts, about three and a half grains for each pound of body weight. The average for women is less than that for men; still less for children, but higher in ratio to their weight than in adults. The excretion of urea varies greatly as a result of differences of diet; it may be raised by an exclusively nitrogenous diet to as high as 100 gm. a day, and greatly lowered by an exclusively vegetable diet. Mental and muscular exercise increase it; rest diminishes it, owing to the consequent alteration of the tissue metabolisms which produce it. Atmospheric changes are said to affect the elimination of urea to almost as great a degree as they alter the excretion of water, as they increase or retard cutaneous activity. Organic disease of the liver diminishes the excretion of urea by diminishing its formation. Acute febrile or inflammatory affections, by increasing tissue waste, increase the elimination of urea, while chronic, cachectic states as a rule have a contrary effect, particularly after a stage of the disease is reached which markedly interferes with alimentation.

Degenerative changes in the kidneys are the most important causes of deficient elimination of urea; such failure on the part of the kidneys often portends serious consequences to the patient in the liability to early development of uræmia. The alarming and dangerous symptoms known by this term are regarded by many recent writers as due not so much to the retention in the blood of urea as of other toxic substances, since it is well known that several times the normal quantity of urea may be present in the blood without injury. The deficient elimination of urea may therefore be regarded as of more importance from a diagnostic point of view than clinically, indicating the probable retention of more toxic substances, as the bile salts, the coloring matters, the xanthins, in whose excretion urea is supposed to assist.

Urea may be obtained in a pure state by the following method: Evaporate about 200 c.c. of urine to a syrupy consistence on a water-bath; allow it to cool, place the vessel containing it in ice water and add an equal volume of pure nitric acid, slowly, while stirring. Let this stand until a mass of brownish crystals is formed, then pour off the fluid and wash the crystals with a very little ice water. Dissolve the mass in alcohol, add animal charcoal which has been washed with hydrochloric acid, filter, evaporate on a water-bath, set aside to crystallize, then filter through muslin and press between heavy filter paper. A mass of pure urea nitrate crystals is thus obtained. To this mass add an excess of barium carbonate and enough alcohol to make a paste; dry, extract with alcohol, evaporate the filtrate, and set it aside to cool. The resulting crystals are nearly or quite pure urea.

Tests for Urea.

Qualitative Tests.—1. The simplest method of detecting urea in solution is to place a drop of the fluid with a drop of pure nitric acid on a glass slip and gently warm. The characteristic rhombic or hexagonal prisms, or plates of urea nitrate may then be seen with a low power of the microscope. The acute angles of these crystals measure 82°. If a strong solution of oxalic acid be used instead of nitric acid, rhombic plates of urea oxalate will be formed.

2. If to a few drops of fluid containing urea an equal quantity of a solution of sodium hypobromite be added, rapid effervescence is produced.

3. Add to the fluids three parts of an aqueous solution of furfur aldehyde (furfurol), then a few drops of strong hydrochloric acid. If urea be present, a series of colors is produced, yellow, green, violet, purple, and red, the precipitate finally settling into a brown sticky mass.

4. *The Biuret Reaction.*—Warm a few crystals of urea in a test tube, add a trace of potassium or sodium hydroxid and a drop of dilute cupric sulphate solution. A rose-red or violet color results.

It should be remembered that while these tests are sufficient for the detection of urea, the result does not denote the presence of urine since urea may be present in many other fluids. If, however, uric acid be also present the evidence may be considered conclusive.

Quantitative Tests.—A great many methods have been devised for the quantitative determination of urea; they are for the most part based on one or other of the three principal methods: 1. Liebig's, or the mercuric nitrate reaction; 2, Knopf's, or the hypobromite; and 3, Fowler's differential density method. Of these the last method has been most simplified and is now most frequently employed.

Liebig's method is based upon the fact that when mercuric nitrate comes into contact with urea in solution, a white precipitate is formed which is insoluble in water and weak alkaline solutions. By using a standard solution of mercuric nitrate and an indicator by which to determine the point at which all the urea has combined with the mercury, it is easy to calculate the amount of urea in the solution. The standard solution of mercuric nitrate is prepared as follows:

Standard Mercuric Nitrate Solution.—Dissolve 77.2 gm. (1158 grains) of red mercuric oxide, previously dried on a water-bath, in dilute nitric acid, evaporate to a syrupy consistence, and gradually add sufficient distilled water to make one litre. Nineteen cubic centimetres of this solution will precipitate the urea in 10 c.c. of a two-per-cent. solution. To facilitate the calculation, 52.6 c.c. of distilled water may be added to the litre of mercuric solution; 20 c.c. of the solution being required to precipitate the urea in 10 c.c. of a two-per-cent. solution, 1 c.c., therefore, representing 1 cgm. of urea.

Since the presence of phosphates and sulphates is liable to cause error, they are first removed by the following solution:

Baryta Solution.—Add one volume of cold saturated solution of barium nitrate to two volumes of cold saturated solution of barium hydrate.

Indicator.—A saturated solution of sodium bicarbonate free from carbonate.

Method of Analysis.—To 40 c.c. of the urine add 20 c.c. of baryta solution and filter. Place 15 c.c. of the filtrate, which now represent 10 c.c. of urine, in a beaker and add to it gradually, from a burette, mercuric nitrate solution, constantly agitating the mixture until a point is reached at which a drop of the mixture when mixed with the indicator (bicarbonate of sodium solution) produces a pale yellow

color. From the quantity of mercuric-nitrate solution which was required to produce this reaction, the percentage of urea is then calculated, each cubic centimetre of the latter solution representing 1 cgm. (0.01) of urea.

Corrections.—1. Since this method does not take into consideration the reaction which is produced by the chlorides of the urine, a correction must be made by subtracting from the result 1 gm. (fifteen grains) of urea for every 1.3 gm. (nineteen grains) of sodium chloride found present in another specimen of the same urine. (See Tests for the Chlorides.) This correction may be approximated, however, by deducting 2 cgm. of urea for every 15 c.c. of mercuric nitrate solution used. 2. The results of this method are accurate only when the percentage of urea is about normal—two per cent. A correction must therefore be made when the quantity is above or below two per cent. When below two per cent., deduct 0.1 c.c. of mercuric nitrate for every 4 c.c. used, before calculating the percentage of urea. If more than two per cent. of urea is found, a second titration must be made after first diluting the urine with half as much distilled water as would equal the quantity of mercuric nitrate solution which was required, over 20 c.c., to complete the reduction. 3. If ammonium carbonate be present, its quantity must be determined by titration with normal sulphuric acid and the result, in terms of urea, added to the result of the former titration, allowing 0.03 gm. of urea for each 0.017 gm. of ammonia.

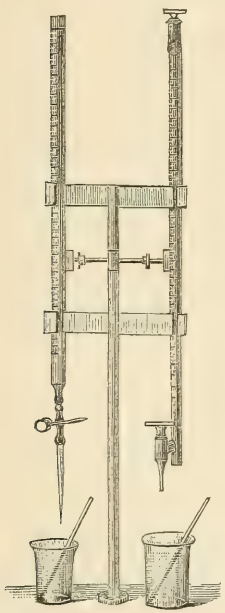

Fig. 45. — Burettes and Beakers for Volumetric Analysis (Tyson).

If albumin be present in the urine, it must first be removed. This is best accomplished by acidulating about 100 c.c. of the urine in a flask with acetic acid and boiling, afterwards restoring the quantity lost by evaporation by the addition of distilled water, then filtering.

Leucin and tyrosin also impair the accuracy of this test by combining with the mercuric nitrate solution; but they are present in such small quantity that they may be ignored, except in conditions, as in acute yellow atrophy of the liver, in which they are known to be greatly increased. Under such circumstances the test may prove useless.

Pflüger's Modification.—The most popular of the several modifications of Liebig's test is that of Pflüger. This consists in first deter-

mining the quantity of sodium-bicarbonate solution which is required to neutralize 20 c.c. of the mercuric-nitrate solution in the presence of urea. To determine this, take 10 c.c. of a freshly prepared two-per-cent. urea solution and add to it, without interruption, 20 c.c. of the standard mercuric-nitrate solution described above. To this add, from a burette, slowly and with constant agitation, sufficient standard sodium-carbonate solution (53 gm. to a litre) to produce a permanent yellow color.

Before proceeding with the test, lay a glass plate on a black cloth and upon it place several separate drops of a thick mixture of sodium bicarbonate and water, to have it in readiness for the next step in the process. Twenty cubic centimetres of the urine are now taken and titrated with the mercuric nitrate solution, and tested from time to time by placing a drop of the mixture on the glass plate, in contact with a drop of the sodium-bicarbonate mixture. As the titration approaches the point of saturation, a drop of the mixture becomes yellow when in contact with the sodium bicarbonate, but the color vanishes when the drops are mixed. The titration is then continued with great care until the yellow color becomes permanent when the drops are mixed.

Now neutralize the mixture, as quickly as possible, by the addition of normal sodium-carbonate solution in nearly the quantity that was found necessary in the preliminary test. After this, add sufficient mercuric-nitrate solution to complete the reaction, the additions being made in tenths of a cubic centimetre with agitation after each addition.

If too much time be consumed in making this test, it will sometimes be found that the mixture assumes a permanent yellow color, while it is still distinctly acid in reaction, even after the addition of the sodium-carbonate solution and without further titration with mercuric solution. This is probably due to the presence of carbonic acid held in solution. Under such circumstances the test must be repeated; in fact, a repetition generally gives better results than those obtained from the first test, since the titration can be more rapidly done.

Correction.—Pflüger's correction is made by subtracting the quantity of mercuric-nitrate solution used from the sum of the urea solution, the sodium-carbonate solution, and whatever other fluids were used, multiplying the remainder by 0.08 and deducting the product from the result of the analysis. If, however, the sum of the other fluids is more than three times as great as the quantity of mercuric-nitrate solution used, the result is still too high.

The Hypobromite Method.—This test depends upon a reaction

which takes place when a solution of urea is treated with a solution of sodium hypobromite, the formula of which is:

$$CON_2H_4 + 3NaBrO = CO_2 + 2H_2O + 3NaBr + 2N.$$

A suitable apparatus is required; the Doremus ureometer is generally used in this country (Fig. 46).

Two reagents are required and may be kept separate for an indefinite time. 1. Sodium hydroxid 100 gm., distilled water 250 c.c. 2. Bromine. Immediately before the test is made, prepare the hypobromite solution by mixing 1 c.c. of bromine with 10 c.c. of the sodium-hydroxid solution, and adding a sufficient quantity of water to fill the long arm of the ureometer (about 40 c.c. are required). The fluids may be mixed in the ureometer.

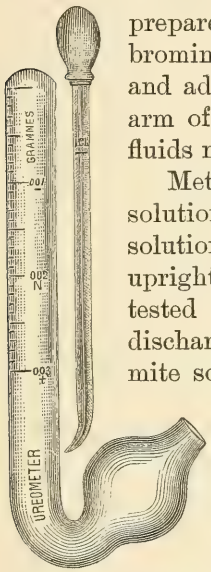

FIG. 46.—The Doremus Apparatus for the Estimation of Urea.

Method: After filling the bulb with the hypobromite solution, the instrument is so inclined as to permit the solution to fill the long arm; it is then restored to the upright position. One cubic centimetre of the urine to be tested is now drawn into the pipette and from it slowly discharged into the bulb so as to mix with the hypobromite solution only at the base of the long arm. A decomposition of the urea is at once set up, the liberated nitrogen collecting in the upright arm of the instrument. Great care must be taken not to occasion too rapid decomposition and consequent escape of the nitrogen. About fifteen minutes are required for the full decomposition of the urea, after which the result may be read from the scale on the instrument. The ureometer may be obtained with either the decimal or the English scale, reading the fraction of a gram of urea to the cubic centimetre of urine, or representing the number of grains in each ounce. The former scale is to be preferred, however, on account of the greater facility for calculating the percentage, 0.02 gm. being equal to the normal two per cent. of urea.

Squibb's Modification.—Although this method is a modification of the last, it may properly be termed the hypochlorite method in contradistinction to it. The advantages claimed for it are that the apparatus required may readily be prepared by the physician and that the Labarraque's solution, which is used instead of the sodium hypobromite, may be more easily obtained and is free from offensive odor. A special apparatus may, however, be purchased. The method of procedure is as follows: After closing the screw clip on the

pendent rubber tube seen in the illustration (Fig. 47) a small test tube containing 5 c.c. of the urine to be tested is placed in the smaller bottle with 25 or 30 c.c. of the test solution—Liquor sodæ chloratæ, U. S. P.; the stopper is tightly replaced and the screw clip is opened. If the apparatus be properly connected, only a few drops of water will escape from the rubber tube. A graduated glass is then placed under the open tube and the urine is caused to mingle with the decomposing solution by tipping the bottle. Since the gas which is evolved displaces its own volume of water from the larger bottle, the quantity of the latter which is found in the graduated glass after

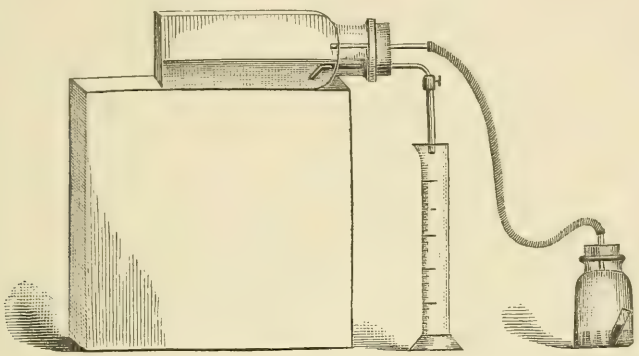

Fig. 47.—The Squibb Apparatus for the Estimation of Urea.

the reaction has ceased will represent the volume of nitrogen. The quantity of water multiplied by 0.00282 gives the quantity of urea present in the 5 c.c. of urine tested.

Fowler's Differential-Density Method.—This method is based upon the reduction of specific gravity which occurs in a specimen of urine when its urea is decomposed by the hypochlorites. Each degree of density lost represents 0.77 per cent. of urea, or about three and a half grains to the fluidounce. The solution of chlorinated soda is used in the test, seven parts of it decomposing the urea in one part of urine, except when the quantity of urea is very large; then the urine should be diluted with an equal volume of distilled water and the result multiplied by two.

About one ounce of urine should be treated with seven times as much of the Labarraque's solution, and two hours should be allowed for the decomposition. To determine the specific gravity of the mixture before the decomposition of the urea, multiply the specific gravity of the Labarraque's solution by seven, add the specific gravity of the urine, and divide the sum by eight. From the result, subtract the specific gravity of the mixture after decomposition. From this

result the percentage of urea is obtained by multiplying by 0.77. The temperature of the three fluids must be the same when their specific gravity is tested, in order to insure accuracy. The presence of albumin or sugar does not interfere with this test.

Uric Acid.

Uric acid ($C_5H_4N_4O_3$) is a weak dibasic acid occurring in the urine as a by-product of the same metabolism as produces urea. In this respect, it belongs to the class of products known as leucomaines of the uric acid, or xanthin group. Sir William Roberts says: "The presence of uric acid in human urine is somewhat anomalous, as it is not needed as a vehicle for the elimination of nitrogen. Its place is taken by urea, which, by its easy solubility, is better adapted to the liquid urine of animals. Perhaps uric acid is a vestigial remnant in mammalian descent. But, although physiologically insignificant, uric acid is pathologically the most prominent component of the urine, chiefly because of its tendency to form concretions."

The quantity of uric acid in the urine is small, about 0.4 to 0.8 gm. in the urine of twenty-four hours. Uric acid requires about fifteen thousand parts of cold water for its solution, but it occurs in fresh urine only in combination with potassium, sodium, or ammonium as acid or neutral urates, the former containing one atom of the base, the latter two; neutral urates are freely soluble, acid urates only sparingly so. Bence Jones claims that uric acid occurs normally in the animal body only in the form of hyperacid combinations which he terms quadrurates; that the acid urates are encountered only pathologically as gouty concretions, and that the neutral urates are known only as laboratory products.

Urates remaining in solution after the urine has become cold are generally neutral and may be precipitated, especially if in excess, by the addition of nitric or other strong acid, the precipitate appearing as a delicate white cloud. In this reaction, the urates may be mistaken for albumin. Acid urates are usually deposited, in part at least, after the urine becomes cold, and are found on microscopic examination as yellowish-red, rhombic, rectangular, wedge-shaped, or whetstone-shaped crystals. Uric acid and its compounds are the only urinary sediments normally having a yellow color. Spontaneous precipitation of uric acid does not signify that it is in excess, unless occurring within from four to six hours after the urine is voided, since it always occurs upon long standing. Earlier precipitation may occur when uric acid is in excess, when the urine is highly acid, or when it is poor in mineral salts and coloring matter.

The seat of uric-acid formation is probably, like that of urea, in the tissues, especially in the liver and spleen. This view receives support by the facts that a small amount of uric acid is found normally in the blood, that when, as in gout, its elimination is diminished, it accumulates in the blood and tissues; that its excretion is most abundant at the period of digestion when the liver is most active, and that its formation continues after extirpation of the kidneys. The theory that it is formed by the kidneys seems to have been based for the most part upon observations on birds and reptiles, the accuracy of which has been called in question. Minkowski made the important observation that, in geese whose livers he had extirpated, the urine, during the few hours in which life was sustained, contained only two or three per cent. of uric acid, instead of the normal sixty to seventy per cent.

The ratio of uric acid to urea in health is more or less constant; Parkes estimates it as 1:45; Ritter places it at 1:36 on animal diet, 1:27.5 on a mixed diet, and 1:22 on vegetable diet. Its production is increased by nitrogenous food, by rest, sedentary habits, a diet which overtaxes the liver, or by defective action of this organ. Increase occurs also in fevers, inflammations, diseases which diminish respiration (oxygenation) or produce leucocytosis; diseases of the lungs or heart, ascites, abdominal tumors, etc.; in leucocythæmia, in hydruria, urina spastica, and in the so-called uric-acid diathesis. The same effect may be produced by the administration of certain medicines. Bohland has recently observed (*Centralblatt für innere Medicin*, No. 3, 1896) that the administration of the salicylates increases both the production and elimination of uric acid, and Weintraud has shown (*Berliner klinische Wochenschrift*, Bd. 32, 1895, p. 405) that the ingestion of substances rich in nuclein produces the same effect.

Uric-acid excretion is diminished in advanced nephritis, in arthritis, and in gout, and symptoms have been attributed to its retention, notably headache, emaciation, and various nervous disturbances, many of which are probably due as well to the retention of other products of the same group.

Uric acid may be obtained by rendering a specimen of urine strongly acid with hydrochloric acid, allowing it to crystallize, then filtering and washing the crystals with cold distilled water. It may be readily recognized under the microscope by the peculiar form and color of its crystals.

Tests for Uric Acid.

Qualitative Tests. 1. *The Murexide Test.*—To a small quantity of the sediment of urine, or to the residue after evaporation, add a

few drops of nitric acid in a porcelain capsule, evaporate over a Bunsen flame to almost dryness, and add a drop or two of ammonia. If uric acid be present, a beautiful purple-red color will appear and diffuse itself with the ammonia.

This reaction depends upon the formation of alloxan and alloxanthin on the addition of nitric acid with heat, which ammonia changes into murexide (acid purpurate of ammonia).

2. *The Silver Test.*—Moisten a piece of white filter paper with a drop or two of silver-nitrate solution, touch the spot with a solution of uric acid made alkaline with sodium-carbonate solution; a black color is produced if 0.001 per cent. of uric acid is present, a gray or brownish-yellow color in the presence of 0.0005 per cent.

3. *The Copper Test.*—A solution of uric acid or of a urate to which a solution of cupric sulphate and potassium hydroxid has been added yields, when warmed, a reddish precipitate of cuprous oxide. This reaction is often observed in making the copper tests for sugar and may lead to error.

Quantitative Tests.—We have no thoroughly reliable method of determining uric acid. The method of Haycraft, until recently almost exclusively used, has been found uncertain and variable in its results. It was based upon the reaction which takes place between uric acid and silver nitrate in solution, forming the urate of silver. This salt was then dissolved in nitric acid, the quantity of silver determined, and from this the uric acid was estimated.

1. *Heintz's Method.*—One of the simplest methods for the determination of uric acid is that of Heintz, as follows: Filter 200 c.c. of urine, add to it 10 c.c. of hydrochloric acid, and let stand for twenty-four hours in a cool place. Collect the uric-acid crystals now formed on a filter previously weighed, wash them with a little cold distilled water, dry the filter and crystals in a desiccator and weigh; subtract from this the weight of the filter: the difference will be the weight of the uric acid in 200 c.c. of the urine. If albumin be present, it must be removed before applying the test. This test sometimes fails, however, owing to the fact that uric acid does not always crystallize out of the solution.

2. *Hopkins' Method.*—This is probably the best of the many recently proposed methods. It consists in converting the uric acid and urates into ammonium urate, separating the uric acid from this, and estimating its quantity by titration with a normal solution of potassium permanganate. The method may be applied with slight modifications to pathological as well as normal urine.

(*a*) In normal urine without deposit: To 100 c.c. of urine add ammonium chloride (about 35 gm.) until no more will dissolve and

a few crystals remain undissolved after repeated stirring. These crystals will nearly or quite all dissolve after the temperature has been restored, but no more need be added.

Let the solution stand for two hours, occasionally agitating it, filter through thin filter paper, and wash three or four times with saturated ammonium-chloride solution. If the filtrate does not remain perfectly clear, repeat the filtration.

Now wash the precipitate off the filter with a stream of hot distilled water into a beaker, add an excess of hydrochloric acid, heat just to boiling, and set aside in a cool place for two hours or longer. Then, if the fluid has become cold, filter and wash with cold distilled water. Before washing, however, measure accurately the filtrate, as 1 mgm. must be added to the final result for each 15 c.c. of the filtrate. This need not, however, exceed 20 to 30 c.c.

Wash the uric acid from the filter with a little hot water, add a little sodium carbonate, and heat until the crystals are dissolved. Add enough water to make 100 c.c., transfer to a flask, mix with it 20 c.c. of pure concentrated sulphuric acid, and immediately titrate with a one-twentieth normal potassium-permanganate solution, constantly agitating the fluid. As soon as a pink color begins to appear, titrate slowly until the color becomes permanent. The standard ($\frac{N}{20}$) solution contains 1.577 gm. of potassium permanganate in a litre of distilled water, and 1 c.c. represents 0.00375 gm. of uric acid.

(*b*) In urine containing cystin, Purdy recommends the addition of a few drops of strong ammonia.

(*c*) In alkaline urine the phosphates, if abundant, should be precipitated by heat and removed by filtration.

(*d*) In albuminous urine, more time should be given to the digestion with hydrochloric acid.

(*e*) In deeply pigmented urine, the original precipitate of urates should be thoroughly digested with alcohol, and after the filtrate has been acidulated it should be gradually heated to boiling and digested for some time on a water-bath. The washing of the crystals should then be thorough.

4. The following is a modification of Arthaud and Butte's test: Add to the urine an excess of sodium carbonate, and filter to remove phosphates; then take a definite quantity of the filtered urine and titrate with the following solution until a precipitate is no longer formed. The solution is composed of cupric sulphate, 1.484 gm.; sodium-potassium tartrate, 40 gm.; sodium hyposulphite, 20 gm.; distilled water, enough to make 1,000 c.c. One cubic centimetre of the solution precipitates 0.001 gm. of uric acid. To determine the completion of the titration, the following indicator should be used:

Potassium ferrocyanide, 1 gm.; hydrochloric acid, 5 gm.; distilled water, 50 c.c. Several drops of this solution are scattered over a white porcelain plate. When titration is complete, a drop of the mixture gives a chestnut-brown color to a drop of the indicator.

Xanthin.

Xanthin ($C_5H_4N_4O_2$) is occasionally found in small quantity in normal urine, not exceeding 1 gm. in 300 litres, and has been found as an ingredient of a rare form of calculus in a young subject. It may occur in urinary sediment as brittle, waxy, yellowish-white scales, soluble in alkalies, feebly soluble in water, insoluble in alcohol and ether. Little is known of the mode of its production, but with the other members of this group it is regarded as a leucomaine.

Detection.—Xanthin dissolved in dilute hydrochloric acid separates into hexagonal crystals on evaporation. If a few drops of urine containing xanthin be mixed with an equal quantity of nitric acid and evaporated to dryness, it yields a yellow residue which is turned red by potassium hydroxid and reddish-purple by heat.

Allantoin.

Allantoin ($C_4H_6N_4O_3$) is a substance closely allied to uric acid and occurs as a mere trace in the urine, except in that from newborn infants. It is increased by a meat diet and by the administration of tannic acid. It may be obtained from uric acid by oxidation with potassium permanganate, providing rise of temperature be prevented during the reaction, the permanganate taking up water and oxygen to form allantoin and carbonic acid. Allantoin crystallizes in colorless prisms, soluble in hot water, slightly soluble in cold water, but insoluble in alcohol or ether.

Detection.—Treat a small quantity of urine with lead acetate and filter, pass sulphuretted hydrogen through the filtrate, filter again, and evaporate the filtrate to a syrupy consistence. Allantoin will crystallize out in the course of several days.

Creatin and Creatinin.

Creatin ($C_4H_9N_3O_2$) and creatinin ($C_4H_7N_3O$) are probably physiologically identical, but both exist in normal urine; creatin is more abundant in alkaline urine, creatinin in strongly acid urine. The latter is therefore considered the normal constituent. It is a strong base, yielding an alkaline reaction to litmus. It crystallizes

in large, colorless prisms, soluble in water and alcohol, sparingly soluble in ether. Creatinin is believed to originate in the muscles, which contain a large quantity of creatin, or it may be derived from meat food. It is probably carried from its source by the blood and eliminated without change. It is about equal in quantity to uric acid, 0.5 to 0.9 gm. in twenty-four hours. It is increased by nitrogenous food, decreased by fasting; increased during the pyrexia of acute diseases, as pneumonia, typhoid and intermittent fevers, sometimes in diabetes, and is diminished in advanced diseases of the kidneys, in tetanus, and usually in diseases characterized by wasting of muscles.

Tests.

Detection.—1. If to a dilute solution of creatinin a solution of sodium nitroprussiate be added, and this followed by the addition of sodium hydroxid, a red color is produced which changes to yellow upon standing. This, Weyl's test, is the most delicate we have for the detection of creatinin.

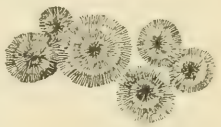

Fig. 48. — Creatinin - Zinc Chloride Crystals.

2. Acidulate the urine with nitric acid and add phosphomolybdic acid; a yellow crystalline precipitate is formed which is soluble in hot nitric acid.

3. Creatinin enters into combination with zinc chloride to form characteristic groups, or rosettes, of fine needle-like crystals. Neubauer employed this reaction for quantitative determination of creatinin, his method, as revised by Salkowski, being the one generally used.

Thiocyanic Acid.

This substance is found in the urine in exceedingly small amounts, always in combination as thiocyanates. It is derived from the saliva.

Aromatic Substances in the Urine—Hippuric Acid.

Hippuric acid ($C_9H_9NO_3$) occurs in only small quantities in human urine (0.5 to 1.0 gm. in twenty-four hours) and, having no clinical significance, so far as is known, is of interest chiefly as an illustration of synthesis occurring in the human organism, since it is formed in the epithelium of the renal tubules. It is found most abundant in the urine of the herbivora, less so in that of the omnivora, and is absent from the urine of the carnivora.

Hippuric acid is best obtained for examination from the urine of a herbivorous animal, the horse or cow. When separated, it exists as colorless, odorless, slightly bitter, rhombic crystals having sharp,

bevelled ends; it is soluble in six hundred parts of cold water, more soluble in hot water, readily soluble in hot alcohol and ether, and in ammonia and alcohol, but insoluble in acetic acid. It is increased in human urine by a vegetable diet, but does not entirely disappear under an animal diet. Certain fruits have a marked effect in causing its increase, as cranberries, greengages, prunes, etc., and the same is true of the administration of certain drugs, as benzoic acid, oil of bitter almonds, toluol, cinnamic acid, and a number of other substances. Some of the febrile diseases, diabetes and cholera, are attended by an increase of hippuric acid in the urine.

Detection.—1. If urine containing hippuric acid be evaporated with nitric acid, and the residue heated in a dry test tube, an odor resembling that of bitter almonds is produced, owing to the production of nitrobenzol.

2. Add a little milk of lime to the urine, boil for a few minutes and filter, to remove the phosphates. Then exactly neutralize by the careful addition of hyrochloric acid, and stirring, concentrate to about one-eighth the original volume, and add an excess of hydrochloric acid. Impure hippuric acid will separate. Dissolve this in hot water, treat with chlorine gas to remove the color, and pure hippuric acid will crystalize out on cooling.

3. Evaporate slightly a small quantity of urine, and acidulate with hydrochloric acid; if hippuric acid be in excess, it will crystallize in the course of about two hours, and may be recognized with the microscope. As the crystals of hippuric acid sometimes assume forms which resemble those of the triple phosphates on the one hand and those of uric acid on the other, owing to an unusual shape of the crystals, their identity should be established by allowing first a drop of acetic acid to flow under the cover-glass and, if solution does not occur, as would be the case with the triple phosphates, add a drop of alcohol, which will dissolve hippuric acid, but not uric acid.

Ethereal Sulphates.

The ethereal sulphates belong to the same group of aromatic substances as hippuric acid. The principal members of the class are the potassium-sulphate compounds of phenol and indol, namely, phenol-potassium sulphate and indoxyl-potassium sulphate. Other members of the group, cresol-potassium sulphate, catechol-potassium sulphate, and skatoxyl-potassium sulphate are of about the same significance and need not receive separate consideration.

The ethereal sulphates are found in small quantities in the urine of all animals, and are believed to be derived either from aromatic

substances ingested with the food, or from the action of the bacteria of putrefaction in the intestines. Hoppe-Seyler found them increased as a result of the putrefaction of food, owing to defective absorption in the intestine during peritonitis and intestinal tuberculosis, and in other diseases causing retention and putrefaction of food; also as a result of putrefactive changes outside of the intestine, as in putrid abscesses, cysts, etc. The putrefaction in the intestines, as Bouchard has shown, results in the formation of indol, the radicle of which, indoxyl, unites with potassium sulphate to form the compound under consideration.

The phenol derivative appears in increased quantity in the urine as a result of the internal or external use of carbolic acid; the indol derivative, after the ingestion of indol, and in Addison's disease, cholera, cancer, typhoid fever, tuberculosis of the intestine and some diseases of the nervous system.

Detection.—Phenol-potassium sulphate ($C_6H_5O.KSO_3$) may be recognized by acidulating the urine with sulphuric acid, then distilling. Phenol appears in the distillate; add bromine water and deep yellow tribromophenol appears. Add Millon's reagent to the filtrate and apply heat; a cherry-red color is produced. Ferric chloride added to the distillate produces a deep violet color.

Indoxyl-Potassium Sulphate.

This substance ($C_8H_6NO.KSO_3$) has been termed urine indican and classed by some authors among the urinary coloring matters because it may be decomposed with the production of indigo blue. It is not, however, identical with vegetable indican; it is probably the substance described by Heller under the name of uroxanthin. The blue, green, or red color of pathological urines is sometimes due to the presence of this substance in various degrees of oxidation.

For the detection of indoxyl-potassium sulphate, add ten to twenty drops of the urine to 4 c.c. of hydrochloric acid, with stirring. If the quantity be normal, only a light yellow color is produced; if in excess, a violet or blue color appears. Heller attributes this color reaction to the presence of two other pigments, namely, urrhodin and uroglaucin. If the yellow color does not appear within two or three minutes in this test there is no excess of the sulphate.

MacMunn's Test.—Boil together equal parts of the urine and strong hydrochloric acid, add a few drops of nitric acid, let cool and shake with chloroform. The chloroform is colored violet, and, on spectroscopic examination, shows an absorption band before *D*, due to indigo blue, and another after *D*, due to indigo red.

Albumin, if present, must be removed before these tests are applied, since hydrochloric acid sometimes produces a blue color by its action on albumin.

Urinary Pigments.

Comparatively little is known of the origin or significance of the normal coloring matters of the urine, either physiologically or pathologically. Bouchard considers them highly poisonous.

Urobilin.

This is the most important of the pigments. It is a dark brown, amorphous, somewhat resinous substance, soluble in water, more freely soluble in alcohol and acids, and in solutions of potassium, sodium, or ammonium hydrate. It is believed to originate from the bile pigment (bilirubin) or the blood pigment (hæmoglobin), or from both. It is found in very small quantity in normal urine. Its quantity is increased in acute febrile diseases, especially in rheumatism, gout, pneumonia, and in those which cause marked destruction of blood cells, such as typhoid and septic fevers; also in chronic constipation, epilepsy, neurasthenia from sexual excesses, other nervous disorders, and in tuberculosis. Hayem regards its increase as a sign of hepatic insufficiency, since it occurs in cardiac and other lesions, producing passive hyperæmia of this organ. It is diminished in anæmia and chlorosis, and during convalescence from severe forms of disease, but increased in intracranial hemorrhages, in hemorrhagic infarctions, in retro-uterine hæmatocele and in extra-uterine pregnancy. Lawson states that the excretion of urobilin is much more abundant in tropical regions than in temperate climates. Mandry regards the persistent presence of large quantities of urobilin for more than two weeks after a cœliotomy an indication of a periuterine effusion of blood. According to Piseuti and Gerhardi the percentage of indican is lowered in disease of the pancreas.

Urobilin is probably identical with the hydrobilirubin of Maly, the urohæmatins of Harley and Scherer, the urophæin of Heller; and the hæmaphæin of Gubler, or, as Jolles expresses it, "the normal coloring matter of the urine is in all probability identical with the highest oxidation product of bilirubin, although normal urine at times contains coloring matters that differ from the normal only in the amount of oxygen they contain."

Detection.—Render the urine alkaline with ammonia, filter, and add calcium or zinc chloride solution to the brownish-red or garnet filtrate; a beautiful green fluorescence may be observed by reflected light. The spectrum of this solution shows a dark absorption band

between *b* and *F* of Frauenhofer's scale. Jolles asserts that only pathological urobilin yields fluorescence in the foregoing test, or the absorption band between *b* and *F*.

Urochrome.

This substance was first described by Thudicum as the yellow coloring matter of the urine. It is closely allied to urobilin, if indeed it is not merely an impure form of it. It occurs in yellowish scales which are soluble in ether and dilute mineral acids and alkalies, sparingly soluble in water, and less so in alcohol. The aqueous solution changes, on standing, to a red color and finally becomes clouded by a flocculent precipitate. Nitrate of silver precipitates it from solution as a gelatinous mass soluble in nitric acid. The simplest of Thudicum's methods of obtaining urochrome was by precipitating fresh urine with lead acetate, filtering and treating the filtrate with sulphuric acid. A body resembling xanthin is also separated along with the urochrome. Mercuric nitrate produces a white precipitate which changes to a flesh color on boiling, the supernatant fluid becoming rose-red.

Uroerythrin.

This is regarded by some authors as an abnormal pigment; by some it is regarded as identical with skatol pigment, but MacMunn has found that it gives characteristic reactions which separate it from other pigments. It is the chief coloring matter of the urates, and may be separated from them by boiling alcohol. Its spectrum consists of two ill-defined bands before *F*.

Oxalic Acid.

Oxalic acid ($C_2H_2O_4$) is found in the urine as calcium oxalate, which is held in solution by the acid sodium phosphate; it amounts to from 0.01 to 0.02 gm. in twenty-four hours, is occasionally absent, and when in excess is precipitated, often before it is voided, in quadratic, octahedral, "envelope" crystals, occasionally in dumbbell forms. Owing to the strong affinity of oxalic acid for lime it probably never occurs in a free state in the urine. It is increased by the ingestion of certain fruits and vegetables, as apples, grapes, tomatoes, rhubarb, cabbage, spinach, asparagus, turnips, etc. It is frequently very abundant in the urine of persons of indolent habits, whose chief aim is the gratification of appetite, especially when indigestion supervenes; it occurs also in the so-called nervous dyspepsia. Its occurrence is often accompanied by pains in the back and loins, intestinal hemorrhage, vesical irritability, incontinence

of urine, and sometimes by hæmaturia due to the direct injury of the urinary passages by the oxalate crystals. By some observers these symptoms are referred to the presence of an excess of oxalic acid in the blood, the origin of which is doubtless due to a derangement of the alimentary canal. (For a more complete description of Oxaluria and the method of quantitative estimation, see Vol. I., p. 634.)

Lactic Acid.

This substance ($C_3H_6O_3$) is of doubtful occurrence in normal urine. It has been observed for the most part as sarcolactic acid, after physiological disturbances and great muscular activity. It is found also in the urine of diabetes, cirrhosis, and acute yellow atrophy of the liver, in leucocythæmia, osteomalacia, rickets, phosphorus poisoning, and trichinosis.

Succinic Acid.

Succinic acid ($C_4H_6O_4$) belongs to the same series as oxalic acid and has been sometimes met with in the urine, especially after the ingestion of asparagus.

Fatty Acids.

Acetic, butyric, formic, and propionic acids are found free in the urine, varying in quantity, according to v. Jaksch, from mere traces to 0.008 gm. in twenty-four hours, the amount depending largely upon the character of the food. In certain hepatic diseases—abscess, cirrhosis, cancer, syphilis—and in fevers, they are sometimes very greatly increased, reaching from 0.006 to a 0.1 gm. in twenty-four hours. Free indulgence in alcohol causes an increase.

Glycerophosphoric Acid.

This occurs in traces in the urine and is said to be increased after chloroform narcosis and in certain nervous disorders.

Mucin.

Mucin is the chief constituent of the mucus secreted by the follicles of the urinary passages. A difference of opinion exists as to its presence in normal urine. While some observers claim that it is a normal ingredient of the urine, others hold that this opinion is based upon faulty analysis, which reveals nucleoalbumin and not mucin;

they are probably identical. When found in considerable quantity in urine which is otherwise normal, the increase probably arises from the passage of the urine over inflamed mucous surfaces. It is precipitated by alcohol, strong vegetable acids, and dilute mineral acids, but it is not precipitated by heat or dissolved by an excess of acetic acid. (For the methods of its detection, see p. 723.)

Nucleoalbumin.

Probably the most valuable and most accurate investigations with reference to this body have been made by Dr. D. D. Stewart, of Philadelphia (*Medical News*, May 5th, and July 14th, 1894). Nucleoalbumin has generally been confounded with serum albumin, mucin, peptone, and the proteoses, some observers considering it identical with one of these, others with another. Stewart has, however, developed several points of difference and methods for its differentiation from each of these bodies except mucin. He regards it as identical with the nucleoalbumin derived from the bile. It may owe its origin to the cells of the urinary passages, but in all probability it sometimes arises from the blood serum of the renal vessels. Whether or not it ever constitutes a pathological ingredient of the urine has not been determined.

The method of its recognition and differentiation may be briefly stated thus: It is not precipitated or removed by prolonged boiling and filtration, but yields a distinct cloud when the urine is treated by the contact method with citric acid, glacial acetic acid, glacial phosphoric, trichloracetic, picric, or nitric acid, and reacts to nearly all the tests for serum albumin except heat and the biuret test. It is also an important fact that heating the urine diminishes the reaction in the acid tests, instead of increasing it. Its failure to respond to the heat test and the biuret reaction serves to differentiate it from serum albumin, globulin, peptone, and the albumoses. From peptone it is further distinguishable by the fact that saturation of hot urine with ammonium sulphate removes all trace of nucleoalbumin.

Animal Gum.

This substance, when found in the urine, is believed to be a product of mucin. It is identical with that of saliva, connective tissue, the synovia, chondrin and colloid cysts, and resembles vegetable gum in that it forms levulic acid when treated with hydrochloric acid. It forms an opalescent solution in water and a sticky precipitate with cupric sulphate or ferric chloride.

Sugar.

1. *Glucose.*—Many recent investigations seem to confirm the original statement of Brücke that normal urine contains a trace of glucose. The quantity is, however, so small as not to invalidate the usual tests for abnormal sugar. The copper tests show little if any change, and do not give the characteristic yellow color.

2. *Milk Sugar* is found in variable quantity in the urine of nursing women and sometimes apparently as a result of pathological conditions of the mammary gland (see p. 733).

3. *Inosite*, or muscle sugar, occurs in the brain, lungs, liver, spleen, and kidneys, and has been found in small quantities in normal urine. It is chiefly of interest, however, in that it occurs in nephritis and diabetes (see p. 732).

Ferments.

Pepsin has been found in normal urine, particularly in that voided in the morning. By its action on fibrin, peptone and all intermediate products (proteoses) may be formed (p. 716). Pepsin is detected by soaking small pieces of fibrin in its solution until the pepsin is absorbed, then removing them to a 0.1-per-cent. solution of hydrochloric acid at blood heat, when they are quickly digested. Traces of a milk-curdling ferment, like rennet, and a diastatic ferment, probably trypsin have been isolated from the urine.

Inorganic Constituents.

The principal inorganic constituents of normal urine are the chlorides, carbonates, phosphates, and sulphates of the bases ammonium, potassium, calcium, and magnesium, the total amount reaching from 9 to 25 gm. daily. Traces of fluorin, silicic acid, and iron are also found, and free carbonic acid, nitrogen, and traces of oxygen. The source of these ingredients is in part the food and in part the metabolic processes and tissue-changes of the organism.

Chlorides.

The chlorides, next to urea, are the most abundant of the solid ingredients of the urine, amounting in twenty-four hours to from about 6 to 10 gm.; sodium chloride is most abundant, potassium and ammonium chlorides occur in only small quantities.

The chlorides are increased in health by the ingestion of much

salt with the food and by muscular exercise. They are diminished in diabetes insipidus and in acute febrile diseases, particularly those attended with serous exudations, and may continue diminished, even absent (as in pneumonia), until the crisis has been reached, then become more abundant, great increase marking the establishment of diuresis, when the exuded serum begins to be picked up.

Tests for the Chlorides.

Detection.—Add to the urine in a large test tube a little nitric acid to hold the phosphates in solution, then a drop of silver nitrate solution; a heavy precipitate of chlorides falls which is soluble in ammonia, but insoluble in nitric acid.

If a standard silver solution (as 1 : 8—a drachm to the ounce) be used in this test, an approximate estimate of the chlorides may be made. If, when a drop or two of the silver solution is added, a flaky, white precipitate is formed and quickly falls to the bottom of the tube, the chlorides are not less than normal in quantity; if only a diffused cloudiness occurs, they are diminished; while, if no precipitation occurs, they are absent.

Quantitative Determination.—1. *Purdy's centrifugal method* is the simplest means of determining the quantity of the chlorides. Ten cubic centimetres of urine are placed in the graduated percentage tube, after the addition of a little nitric acid, and the tube is filled to the 15 c.c. mark with the standard silver-nitrate solution. The tubes are then placed in the centrifuge and revolved at the rate of about one thousand revolutions a minute for three minutes, or until the precipitate has been tightly packed into the bottom of the tube. The percentage may then be calculated from the height of the precipitate on the scale. If the hand centrifuge be used, a smaller quantity of urine must be used, owing to the smaller size of the tubes.

2. *Mohr's Method.*—The following solutions are used: (1) A standard silver-nitrate solution, made by dissolving 29.075 gm. of pure nitrate of silver in 1,000 c.c. of distilled water, each cubic centimetre of which will precipitate 10 mgm. (0.010) of sodium chloride; and (2) a saturated aqueous solution of neutral potassium chromate.

Dilute 10 c.c. of urine with 100 c.c. of distilled water, and add a few drops of the potassium-chromate solution. Then drop into this from a burette the silver solution. A white precipitate of silver chloride is formed until all the chlorides have been precipitated, then a red precipitate begins to form, consisting of silver chromate. As soon, therefore, as the pink color appears, after agitating the mixture, the quantity of the silver solution that has been used is read and a calculation is made of the quantity of chlorides in the 10 c.c.

of urine, from which the percentage is readily determined. One cubic centimetre should be deducted, however, from the quantity of silver solution used, to offset the other substances found in the urine which unite with the silver more readily than does the potassium chromate.

3. *Sutton's Modification of Mohr's Method.*—Add 1 gm. of pure ammonium nitrate to 10 c.c. of urine in a thin porcelain capsule and evaporate to dryness, then gradually heat over a flame to low redness until all vapor ceases to rise and the residue becomes white. Dissolve this residue in a small quantity of distilled water and neutralize the carbonates present by the addition of dilute acetic acid, then add a few grains of pure calcium carbonate to neutralize any free acid and a drop or two of potassium chromate solution. Titrate the mixture with a decinormal silver-nitrate solution made by dissolving 16.955 gm. of silver nitrate in 1,000 c.c. of distilled water until a pink tinge appears. Each cubic centimetre of this solution represents 0.005837 gm. of sodium chloride.

Phosphates.

Phosphoric acid (H_3PO_4) is excreted in normal urine in the quantity of from 1.5 to 2.5 gm. in twenty-four hours; about one-third of this is combined with the alkaline earths, calcium and magnesium (earthy phosphates), and two-thirds with the alkalies, sodium and potassium (alkaline phosphates).

The *earthy phosphates* are insoluble in water, but are dissolved by acids. They are the phosphates of calcium and magnesium, the former being the more abundant, the ratio of calcium to magnesium being about as 67 to 33. They are held in solution in acid urine, but are precipitated in alkaline urine, the precipitation becoming more rapid on the application of heat. This precipitation may be distinguished from that of albumin, which it resembles, by the addition of a little acid to the urine, causing the phosphates to redissolve.

The acid phosphate of magnesium forms a combination with ammonium in the alkaline fermentation of the urine which is known as the triple phosphate, or *ammonium-magnesium phosphate* ($MgNH_4 \cdot 6H_2O$); these may be recognized on microscopic examination of the sediment by their characteristic feathery, snowflake, stellate, or fern-leaf appearance, assuming, when mature, a quadrangular, "coffin-lid" form.

The *alkaline phosphates* exist in the blood, according to Ralfe, as neutral phosphates (hydrogen-disodium phosphate—HNa_2PO_4), but appear in the urine as acid phosphates of sodium and potassium (dihydrogen-sodium phosphate—H_2NaPO_4), the sodium phosphate

being the more abundant. To these salts is due the acid reaction of normal urine. They are soluble in water and in alkaline fluids, and are about twice as abundant in the urine as are the earthy phosphates. Their quantity depends, however, largely upon the character of the food, being increased by a nitrogenous diet.

The phosphates are excreted in diminished quantity in most forms of renal disease, especially in functional disorders and acute diseases; also in chronic articular rheumatism, gout, the intervals of intermittent fever, and during pregnancy.

The phosphates are increased in extensive destructive lesions of bone, as rickets, osteomalacia; in phthisis, acute yellow atrophy and cirrhosis of the liver, leukæmia, severe anæmia, and in diseases affecting the nerve centres; they may be increased by disturbances of digestion ("flatulent dyspepsia"). That an increase follows mental activity has been asserted, but has not been demonstrated. The potassium phosphate is the more abundant in fevers. The triple phosphates are found usually when the urine undergoes ammoniacal decomposition in the bladder as a result of cystitis or other disease of the urinary passages.

Phosphatic diabetes is the name given to a condition first described by Teissier in which continued increased excretion of the phosphates, amounting at times to from 7 to 9 gm. in twenty-four hours, is attended by symptoms resembling those of diabetes, progressive emaciation, abnormal appetite, dry skin, a tendency to furunculosis, and pains in the loins and pelvic region.

A spontaneous deposit of the phosphates does not of necessity denote an excessive excretion. This can be determined only by calculating the entire quantity found in the urine of twenty-four hours.

Tests for the Phosphates.

Detection. Earthy Phosphates.—Render the urine strongly alkaline with sodium, potassium, or ammonia and gently warm. The earthy phosphates are precipitated in a whitish cloud which soon settles. The precipitate is dissolved on the addition of acetic acid. The white color of the earthy phosphates may be altered by the presence of a large amount of urinary coloring matter, blood, or bile pigment in the urine.

If this test be made in a test tube of 2 c.c. diameter, Hofmann and Ultzmann have shown that a precipitate 1 cm. high, after settling, indicates a normal quantity of earthy phosphates; if it is 2 or 3 cm. high, they are increased; if only a cloudy or flaky precipitation occurs, they are deficient.

Alkaline Phosphates.—The earthy phosphates are first removed by

precipitation with potassium, sodium, or ammonia and by filtration. To the filtrate add one-third its volume of magnesium fluid, consisting of magnesium sulphate and ammonium chloride, each 1 part, distilled water 8 parts and pure liquor ammoniæ 1 part. The alkaline phosphates are precipitated in a white cloud. According to Hofmann and Ultzmann, if they are normal in amount, only a milky turbidity should be produced; if the precipitate be so copious as to produce a creamy appearance, they are increased; if only a very slight turbidity, they are diminished.

The percentage of either the earthy or alkaline phosphates may be more accurately determined with the aid of centrifugal precipitation.

Quantitative Determination of Total Phosphoric Acid.—The following modification of Sutton's method of determining the total amount of phosphoric acid eliminated in the urine is recommended by Purdy. The following solutions are required:

1. A standard solution of uranium nitrate, containing 20.3 gm. of pure uranium nitrate in 1,000 c.c. of distilled water; 1 c.c. corresponds to 5 mgm. of phosphoric acid.

2. A sodium acetate solution, containing 100 gm. of sodium acetate in 900 c.c. of distilled water, to which 100 c.c. of acetic acid are added.

3. A saturated solution of potassium ferrocyanide.

Pour 50 c.c. of urine into a beaker and add 5 c.c. of sodium acetate solution; warm the mixture over a water-bath and add, drop by drop from a pipette, the uranium solution so long as a precipitate is formed. When it becomes difficult to recognize the reaction, the mixture should be thoroughly stirred and a drop of it taken and placed on a plate in contact with a drop of the ferrocyanide solution. If a reddish-brown color is produced at the line of contact, the titration is complete; if no color appears, the beaker must be again warmed and the process continued until the desired reaction can be obtained. From the number of cubic centimetres of the uranium mixture used the percentage and quantity of phosphoric acid can be readily calculated, each cubic centimetre of the solution representing 0.005 gm. of phosphoric acid.

This test may also be employed for the determination of the total quantity of the earthy and alkaline phosphates, as follows:

The earthy phosphates are precipitated from 200 c.c. of urine with ammonia and, after standing twelve hours, are removed by filtration. The precipitate is washed with ammonia water (1 : 3), the filter punctured, and the precipitate washed through by a stream of warm distilled water, and dissolved while warm with the smallest possible

quantity of acetic acid. Then add 5 c.c. of sodium-acetate solution and sufficient distilled water to make 50 c.c. and proceed according to the above test for the total phosphoric acid. The result indicates the percentage of phosphoric acid in combination with the earthy bases, and the difference between this result and that obtained from the estimate of the total phosphoric acid will represent the percentage of phosphoric acid in combination with the alkalies.

Sulphates.

The sulphates are derived for the most part from the proteids. The nitrogen of the proteids, as has been stated, is excreted as urea and uric acid; the sulphur becomes oxidized into sulphuric acid and appears in the urine in combination with sodium and potassium and in part in the ethereal sulphates to which reference has been made. The sulphates, owing to their great solubility, always remain in solution and are not found in the urinary sediment. They amount to from 1.5 to 3 gm. in twenty-four hours, the sodium sulphate predominating.

The sulphates are increased in quantity physiologically after the ingestion of sulphuric acid or its salts, after an exclusive meat diet, muscular exercise, or the inhalation of oxygen gas. They are pathologically increased in acute fevers and notably in rheumatism and in inflammation of the brain or its meninges. A close relation exists normally between the percentage of sulphates and that of urea.

Tests for the Sulphates.

Detection.—Acidulate about 10 c.c. of urine in a test tube with a few drops of hydrochloric acid, and add one-third the volume of barium-chloride solution. A milky white precipitate (barium sulphate) denotes a normal quantity of sulphates; a creamy, heavy precipitate denotes an increased quantity, a faint cloudiness, a diminution of the sulphates.

Quantitative Determination.—1. Into the graduated tube of the centrifuge place 10 c.c. of the urine and fill the tube to the 15 c.c. mark with acid barium-chloride solution consisting of barium chloride 4 parts, hydrochloric acid 1 part, distilled water 16 parts. Thoroughly agitate the tube, replace it, and revolve at the rate of about one thousand revolutions a minute for three minutes. The normal precipitation is about one per cent.

2. The following reagents are required: (1) A standard solution of barium chloride containing 30.5 gm. of crystallized barium chloride in 1,000 c.c. of distilled water; each cubic centimetre of this

solution represents 0.01 gm. of anhydrous sulphuric acid (SO_3). (2) A twenty-per-cent. solution of potassium sulphate. (3) Pure hydrochloric acid.

Analysis.—Acidulate 100 c.c. of the urine with 5 c.c. of hydrochloric acid and heat in a flask to boiling. Then add the barium solution from a pipette so long as a precipitate is formed, being careful to avoid an excess. In order to guard against this, the effect must be tested after every addition of 5 to 8 c.c. of the solution, the mixture being heated before each addition. For example, from 5 to 8 c.c. of the solution are added, and the precipitate is allowed to settle; a few drops of the clear supernatant fluid are then withdrawn in a pipette and treated with a few drops of the barium solution in a watch-glass. If a precipitate is formed, the whole is returned to the flask, heat is applied, and another addition of barium solution is made, this process being repeated until a precipitate is no longer perceptible. If an excess has been added, on the other hand, the analysis must be repeated. To determine this, a drop of the clear supernatant fluid in the flask is mixed with a drop of the potassium sulphate solution; if more than a faint cloudiness is produced, an excess has been added.

The percentage of sulphuric acid is readily calculated from the quantity of the barium solution used, each cubic centimetre representing 0.01 gm. of sulphuric acid.

Carbonates.

The carbonates and bicarbonates of sodium, magnesium, and potassium are found in normal alkaline urine. Their source is the food, particularly fruits and vegetables containing lactic, tartaric, malic, succinic, and other vegetable acids. Urine containing a large amount of carbonates is turbid when voided, or soon becomes so. The precipitate after standing consists chiefly of calcium carbonate, frequently associated with phosphates. Ammonium carbonate is often found in great quantity as a result of the decomposition of urea (alkaline fermentation) in the bladder or after standing.

Tests for the Carbonates.

Detection.—The addition of an acid to urine containing carbonates liberates a colorless gas (carbonic acid) which renders baryta water or lime water turbid.

Quantitative Determination.—The following method of determining the amount of free carbonic acid in the urine was devised by Marchand. One hundred cubic centimetres of urine are placed in a flask

provided with a closely-fitting stopper having two perforations. A tube is passed through one opening until it dips into the urine and is connected by its other end with a tube containing quicklime. One arm of a doubly bent tube is passed through the other opening, but not deep enough to reach the urine, the other arm being passed into an empty flask. The empty flask is then connected in the same manner with three other flasks containing baryta water, the entering tube of each flask dipping into the baryta water and all connections are hermetically sealed.

The urine is then heated to boiling on a water-bath; any portion of it which boils over goes into the empty flask, and the carbonic acid which is driven off passes through the baryta water, forming a precipitate of barium carbonate. Air is now drawn through the apparatus, its passage through the tube containing quicklime freeing it from possible carbonic acid. The barium carbonate is now collected on a filter, washed with distilled water, dissolved with hydrochloric acid, and precipitated as barium sulphate with sulphuric acid. This is dried and weighed, and from it the amount of carbonic acid is calculated, 232.62 parts of barium sulphate representing 196.65 parts of barium carbonate, or 44 parts of carbonic acid.

This method may be employed to determine the total amount of carbonic acid, the urine being first strongly acidulated with hydrochloric acid in the flask. The quantity of combined carbonic acid may then be calculated by subtracting the amount of free carbonic acid from the total amount.

Other Inorganic Constituents.

Small quantities of iron, free ammonia, and hydrogen dioxide are found in the urine. The hydrogen dioxide may be recognized by its giving a blue tinge to tetra paper, and by its bleaching a dilute solution of indigo in the presence of a ferric-sulphate solution.

Gases.—The gases of the urine are, oxygen, 0.2 to 0.6 volume; carbonic acid, four to nine volumes free, two to five volumes combined; nitrogen, 0.7 to 0.8 volume. These may be withdrawn by means of the air pump.

ABNORMAL URINE.

Physical Properties.

The changes in the physical properties of the urine which result from pathological conditions have been considered under the head of physical properties of normal urine, since to consider them here

would necessitate much repetition. The reader is therefore referred to pages 667 to 677, under the titles, Color, Translucency, Specific Gravity, etc.

Chemical Properties.

Proteids.

The kidneys of an individual in perfect health do not permit the escape of an appreciable quantity of proteid substances. The slight trace of nucleoalbumin which seems to be normally present comes for the most part, although possibly not always, from the epithelium of the tubules, and enters the urine after it has left the glomeruli. Under certain pathological conditions, either of the proteids of the blood, serumalbumin, serumglobulin, fibrin, or hæmoglobin, may appear in the urine, singly, or in various combinations. The abnormal condition leading to their escape may be located in the kidneys or in the blood; or it may be a systemic defect. In like manner peptone and certain of the proteoses may escape. Egg albumin may be eliminated through the kidneys after the free ingestion of eggs.

Albumin.

Greater attention has been paid to the subject of albuminuria than to any other abnormal state of the urine. For many years following Bright's discovery of its relation to disease of the kidneys, the term was regarded as synonymous with the term Bright's disease, which was used to designate all forms of renal disorder. Of late years, however, as a result of more accurate clinical and pathological observation, the presence of albumin in the urine has come to be regarded as a symptom common to many affections, not of the kidneys alone, but oftentimes conditions of the blood, or of the blood pressure, or abnormal states of the general system. A great deal has been written in the last few years, indeed, in defence of a so-called physiological albuminuria, many cases being cited to show that albumin sometimes appears in the urine without any coincident lesion to account for its presence and without discoverable impairment of health. A majority of the advocates of this theory have endeavored in reality to prove the absence of other symptoms, particularly the absence of renal casts, which commonly accompany albuminuria from renal disease. While it cannot be denied that albumin is sometimes found in the urine, temporarily, intermittently, or more or less constantly, without discoverable cause, there is much objection to the use of a term in the description of such phenomena which implies

strict conformity to health, as all physiological processes are understood. In the strict use of the term, therefore, there can be but two instances in which the presence of albumin in the urine can be considered physiological; these are, first, the slight trace of nucleo-albumin more or less constantly present; and, second, the elimination of egg albumin, to both of which reference has been made in the preceding paragraph.

But, although the presence in the urine of a small quantity of serumalbumin does not necessarily imply an appreciable lesion of the kidney, since the contrary has been repeatedly demonstrated, nevertheless the discovery of an albuminuria, no matter how slight, should be looked upon as strongly indicative of a renal defect, an alteration of the glomerular basement membrane, if not a more pronounced structural lesion. In the absence of all indications of structural lesions, the albuminuria may be provisionally referred to an alteration of the blood or of the blood pressure, or to an abnormal state of the system. If continued for any length of time, even intermittently, it always denotes some departure from health.

Clinical Significance.—Every form of inflammatory or degenerative disease of the kidneys is more or less constantly accompanied by albuminuria; but the intensity of the latter symptom is not an index to the character or gravity of the disease. The presence of a large quantity of albumin (it rarely exceeds three per cent. by weight) is indicative of a grave lesion, such as acute or chronic exudative or diffuse nephritis; but in the granular kidney (chronic interstitial nephritis), one of the most dangerous of renal degenerations, albumin is rarely abundant, and may be temporarily absent from the urine. The age of the individual is of value in this connection, since interstitial nephritis occurs for the most part after middle life; yet it has been encountered in childhood.

In the so-called *hæmatogenic albuminuria*, the blood is so altered as to increase the diffusibility of the albumin and to permit its escape from the vessels of the glomerulus. This occurs for the most part in profound anæmia, particularly in that of tuberculous patients, the albuminuria frequently occurring before the tuberculous disease can be recognized by physical methods of examination. In some of the infectious diseases, notably scarlatina, diphtheria, and typhoid fever, possibly including tuberculosis, the escape of albumin is believed to be directly due to the presence of micro-organisms in the blood or tissues, or to the action of their toxins on the kidneys (toxic albuminuria). Alcohol, lead, mercury, and phosphorus are included among the causes of this form of albuminuria.

Some authors make a separate class of "*febrile*" *albuminuria*, at-

tributing the presence of albumin to the elevation of temperature, even in the early stages of the infectious diseases. Its causation is supposed to be similar to that which sometimes follows severe muscular exercise, namely, the increased elimination of waste products. It is safe, however, to regard the albuminuria of the later stages of infectious diseases, like that which results from scarlatina, as due ultimately to a degeneration of renal epithelium.

Albuminuria arising from changes in the blood pressure of the kidney may be produced by influences which cause either an increased flow of arterial blood into the kidney, or an interference with the escape of venous blood. An example of this is seen in the albuminuria of heart disease, as from hypertrophy, with or without valvular lesion, a form usually terminating in marked renal degeneration. Most of the so-called *functional albuminurias* are probably of this character, including many cases of violent or prolonged muscular exertion, as in soldiers on forced marches, overworked laborers, and in children after violent exercise. Albuminuria of this character may arise also from an engorgement of internal vessels produced by the action of cold on the body surface, from renal venous thrombosis, from vasomotor disturbance of the renal circulation, from mental worry or fatigue, or from such disease of the nervous system as epilepsy, hysteria, etc. Closely related to this class of etiological factors is the increase of tension in the kidney itself which is produced by congestion and maintained by exudative changes and which Reginald Harrison regards as of importance in continuing the escape of albumin.

Pavy has given the name *cyclic albuminuria* to cases in which the appearance of albumin in the urine is intermittent in character, following a regular daily course, disappearing during sleep, increasing with activity, or occurring in a cycle of from twelve to thirty-six hours' duration. Such cases are most frequently encountered in young male subjects, often, according to Teissier, the offspring of gouty or arthritic parents, and probably belong to the same category as Moxon's *albuminuria of adolescence*. Some, however, regard cyclic albuminuria as only a periodic nucleoalbuminuria, and Ribbert refers the albuminuria of adolescence to a temporary return to an embryonic type on the part of the kidney, basing his theory on the fact that the embryonic kidney secretes albuminous urine up to the time of birth and sometimes fails to arrest its secretion at that time. In all this class of cases the quantity of albumin is usually comparatively small, 0.1 to one per cent., or less. Other features are, a high specific gravity—1.024 to 1.030—the absence of casts, often an increased acidity and increase of urea, urates, and coloring matter, little or no impairment of health,

and no structural lesions. The presence of casts, even of a few hyaline casts, or other features than those enumerated, should be regarded as of serious import in this class of cases.

A. Robin has described, under the name of *phosphatic albuminuria*, a form which he attributes to a destruction of blood cells, associated with marked increase of the phosphoric acid in the urine.

Shattuck ascribes the occurrence of albuminuria in the aged to a senile degeneration, thus accounting for its frequent occurrence in old persons.

Albuminuria sometimes occurs in diseases affecting the skin, such as scabies, or follows the application of a blister. Huchard, Créquy, and others of the Société de Thérapeutique, Paris, have recently strongly condemned the use of vesicatories on this account.

Finally the urine is sometimes rendered albuminous after it has left the kidneys by contamination with the products of inflammation in the renal pelvis, ureters, bladder, or urethra, or with blood from any source. It need hardly be added that more than one of the causes above enumerated may operate simultaneously in producing albuminuria.

Diet has a marked influence upon the quantity of albumin lost in a case of nephritis, but the propriety of regarding this fact in treatment has recently been questioned on the ground that an injury is done in many cases by too great restriction of diet.

Detection. 1. *Heat.*—Fill a test tube a little more than half full of urine and apply heat to the upper portion of the column, or to the entire column, until boiling occurs. If a cloudiness is produced, add a few drops of nitric acid. If, on the addition of the acid, the precipitate remains or becomes more pronounced, it indicates albumin; if it disappears, it denotes the earthy phosphates. An excess of the acid should be avoided, as a soluble acid albumin may be formed. Only a few drops of acid should at first be added, then more, repeating the boiling after each addition, until a precipitation occurs or from twenty to thirty drops have been added.

If the urine to be tested be alkaline in reaction, it should be rendered acid before applying heat, by the addition of a few drops of nitric acid.

This test is one of the most reliable, but it reacts to globulin and mucin, and albumose is precipitated by it after the urine has become cold. Pine acids, if present, as they may be after the administration of cubebs or copaiva, are precipitated, but they may be readily identified by the fact that the precipitate is at once dissolved by alcohol.

2. *Nitric Acid.*—Heller's nitric-acid test is performed by floating a column of urine over a column of pure nitric acid in a test tube.

The tube may be inclined so as to permit the urine to flow very gently over the surface of the acid without mixing, or the urine may be first placed in the tube and the acid placed beneath it by means of a pipette. If albumin be present, an opalescent zone is formed at the point of contact between the acid and urine, varying in depth of whiteness with the abundance of albumin. If no such zone be visible upon examining the tube in a good light over a black background, the test tube should be set aside for an hour or two and examined at intervals of fifteen minutes during that time. It should be remembered, however, that albumose and nucleoalbumin may separate from a cold acidulated urine, and that a slight turbidity thus obtained does not necessarily imply the presence of albumin.

Slightly warming the urine before making this test renders the reaction more certain and prompt, and that of nucleoalbumin less apt to occur. The addition of acid to hot urine, on the other hand, may vitiate the test, particularly if the phosphates be increased, as it may lead to the formation of a soluble alkaline albuminate, by partially acidifying the phosphates and causing the albumin to unite with the remainder.

If the urine be very strongly acid in reaction, the test sometimes fails and should be repeated after carefully neutralizing the urine or after rendering it slightly acid with acetic acid.

In the presence of a large percentage of urates, a slight, usually brownish cloud may be produced by this test, owing to a precipitation of amorphous urates; the cloudiness does not occur, however, at the point of contact between the two fluids, but higher up; it is also more diffused than the cloud due to albumin, extending further up into the urine, and it disappears upon the application of heat.

The cloudiness produced by this test in the presence of mucin occurs higher up in the column of urine, since mucin is soluble in strong nitric acid and precipitated by the dilute acid.

All modifications of albumin are revealed by this test, but no reaction is produced with peptone or the vegetable alkaloids.

When only a small quantity of urine is available, the test may be made in a pipette, as suggested by Dr. A. C. Ewing, of Salt Lake City. A little of the urine is first drawn up into the pipette, then a little pure nitric acid. A distinct zone is formed at the junction of the two fluids.

3. *Purdy's Heat and Acid Test.*—Have on hand a filtered saturated solution of sodium chloride. Add enough of this to the urine to raise the specific gravity ten or fifteen degrees, to prevent the reaction with mucin. Then fill a test tube two-thirds full with the urine, add one or two drops of strong acetic acid and boil the upper inch of the urine

for about half a minute. Examine in a good light, and if albumin be present, it will appear in the upper boiled portion as a more or less milk-white turbidity, according to the quantity present. This test is especially valuable for the detection of minute quantities of albumin.

4. *Potassium-Ferrocyanide Test.*—Pour into a clean test tube from fifteen to thirty drops of acetic acid, add to it two or three times as much of a five-per-cent. solution of potassium ferrocyanide, and mix thoroughly by shaking. Then fill the test tube two-thirds full of the urine to be tested. Albumin, if present, will be precipitated as a more or less milky, flocculent precipitate throughout the entire column, the density corresponding to the quantity of albumin. To facilitate the recognition of the precipitate, the urine so tested should be compared with a specimen of the same urine in a clean test tube of the same size against a dark background, a very faint reaction thus becoming apparent.

It is essential that this test be performed in the manner described or by first mixing the urine and the ferrocyanide solution; the acid must not be added first. When thus performed, it is one of the most valuable of the tests for albumin, invariably revealing all forms and modifications of albumin, acid or alkaline, including nucleoalbumin, and nothing else. It yields no reaction with mucin, urates, phosphates, peptone, vegetable alkaloids, or the pine acids. No precautions are necessary further than to follow the method just described.

The foregoing tests are so delicate, so positive, and so easily performed that no others need, as a rule, be resorted to. It is better that two or three of them be familiarized for use in routine work, to the exclusion of all others. The following tests are given, therefore, chiefly for the sake of reference, and are valuable for the most part when they fail to produce a reaction.

5. *Spiegler's Test.*—This is one of the most sensitive tests, revealing one part of albumin in 150,000 of urine. Whittaker esteems it as one of the most valuable for detecting pre-tuberculous albuminuria.

Add a few drops of hydrochloric or nitric acid to the urine and filter to remove mucin. (Spiegler used acetic acid.) A test tube is now half-filled with the reagent which consists of bichloride of mercury, 4 gm.; tartaric acid, 2 gm.; distilled water, 100 c.c.; glycerin 10 c.c. (or sugar 10 gm.). The urine is flowed gently over this fluid, and, if albumin be present, a white ring will appear at the point of contact.

If the urine contain iodine, a reaction similar to that of albumin is produced. It has been claimed also that the delicacy of this test depends upon the presence of chlorides in the urine, and that its action is slow when these are reduced in quantity to one-fourth the

normal, and that it fails entirely if they be reduced to one-eighth or less.

6. *Potassium-Mercuric-Iodide Test.*—The following solution is used: Potassium iodide, 3.32 gm.; mercuric chloride, 1.35 gm.; acetic acid, 20 c.c.; distilled water enough to make 100 c.c. The potassium iodide and mercuric iodide are dissolved separately in sufficient water, the solutions mixed, the acetic acid is added, with sufficient water to make 100 c.c. A little of the reagent is then poured into a test tube and urine is gently poured over it, as in the other contact tests. The test is very sensitive to albumin, but reveals all modifications of albumin, peptone, proteoses, mucin, and the pine acids.

7. *Picric-Acid Test.*—Sir George Johnson's picric-acid test is made thus: A saturated solution of picric acid (six or seven grains dissolved in an ounce of boiling distilled water) is kept on hand. A test tube is nearly filled with the urine to be tested, and a little of this solution is gently poured upon its surface. If albumin be present, a cloud forms in the area in which the two fluids mingle. Slight mixture must take place in order to bring out the reaction. Albumin, mucin, peptone, proteoses, and vegetable alkaloids respond to the test, but all except albumin and mucin are dissolved by heat. Heat often gives this test an apparently more intense action, but Kirk claims that this is due to a precipitation of mucin, and that it does not add to its efficacy as a test for albumin.

8. *Acidulated-Brine Test.*—One part of strong hydrochloric acid is added to sixteen parts of a saturated solution of sodium chloride, and the urine is flowed upon the mixture in the usual manner. An opaque zone at the junction of the two fluids indicates the presence of albumin.

9. *Trichloracetic Acid.*—To about 2 c.c. of urine fifteen drops of a thirty-per-cent. solution of trichloracetic acid are added. A cloudiness corresponding to the quantity of albumin is produced. Confusion which sometimes arises from a precipitation of the urates, when abundant, may be removed by heat.

This test may be performed by the contact method, or by dropping a small crystal of the acid into 1 c.c. of the urine, previously filtered, in a narrow test tube. The acid dissolves and a line is formed between it and the urine. Dilution of the urine with distilled water prevents to some extent the precipitation of the urates. Remarkable delicacy is claimed for the test, even the detection of 0.002 per cent. of albumin.

10. *Metaphosphoric-Acid Test.*—This test is made in the same manner as the preceding, a small mass of the acid being dropped into the

urine; a milky zone forms as it dissolves. The chief objection to the test lies in the difficulty of keeping the acid.

11. *Sodium-Tungstate Test* (Dr. George Oliver).—Mix equal part of a sodium-tungstate solution (1:4) and a saturated citric-acid solution (10:6), and apply by the contact method. Albumin, mucin, peptone, and urates are precipitated, all dissolving on the application of heat except albumin and mucin.

12. *Nitric-Magnesium Test* (Roberts).—One part of strong nitric acid is added to five parts of a saturated solution of magnesium sulphate and the test is applied by the contact method.

13. *Biuret Test.*—A solution of caustic potash is added to the urine, then a weak solution of cupric sulphate, drop by drop, from a pipette. If albumin be present, the greenish precipitate (cupric peroxide) is redissolved and the fluid assumes a reddish-violet color. Albumose and globulin yield the same reaction, peptone gives a red color.

14. *Millon's Test.*—Millon's reagent is a solution of mercuric nitrate containing an excess of nitric acid. Dissolve one part of mercury in two parts of nitric acid of 1.42 specific gravity and dilute with two volumes of water. To one drachm of urine add ten minims of the reagent. If albumin be present in considerable quantity, a whitish precipitate forms which becomes red when heated; if only a trace of albumin be present, the red color is produced without precipitation. The test reacts also to members of the aromatic series and to some of the benzol group.

15. *Acetic-Acid-Sodium-Sulphate Test.*—Strongly acidulate the urine with acetic acid. To this add one drachm of a strong sodium-sulphate solution and boil. If albumin be present, a permanent precipitate is formed.

16. *Phenic-Acetic-Acid Test* (Millard).—The agent used is composed of glacial phenic (ninety-five per cent. carbolic) acid ʒ ij.; chemically pure acetic acid, ʒ ij.; liquor potassæ, ʒ vi. The test is made by the contact method. Albumin, mucin, peptone, vegetable alkaloids, and pine acids are precipitated by the test; the alkaloids and peptone are dissolved by heat, pine acids by alcohol.

17. *Hynsius' Test.*—Strongly acidulate the urine with acetic acid, add a few cubic centimetres of a saturated solution of sodium chloride and boil. Albumin is indicated by a flocculent precipitate.

18. *Alcohol Test.*—The following test is recommended by Dr. John G. Truax as a fairly delicate test for both albumin and mucin. A test tube is filled to the depth of an inch or more with ninety-eight per cent. alcohol and upon this is dropped a little urine from a pipette passed down nearly to the surface of the urine. If albumin is present,

it is precipitated in a whitish streak extending quickly to the bottom of the tube; if mucus be present, a general cloudiness of the alcohol results. If the alcohol be overlaid with the urine by the contact method, a white ring denotes albumin, and a general cloudiness mucin.

19. *Xanthoproteic Reaction.*—Add to the urine concentrated nitric acid and boil. After the liquid has cooled, add ammonia. If albumin be present, an orange color is produced.

20. *Test Papers and Tablets.*—Test papers have been made by saturating white, chemically pure blotting paper in solutions of the various reagents used in testing for albumin. These papers are cut into strips and dried, and may be carried in the pocket case. The test is made by placing one of the papers in a small test tube with about a drachm of distilled water. After a moment's agitation the paper is removed and the urine added, preferably by the contact method. The ferrocyanide test is one of the best for this method.

More recently, compressed tablets have been introduced for the same purpose and may be used in the same manner.

Many other tests have been proposed, but few, if any of them, possess advantages over those that have been mentioned. Many of them, as indeed many of those already given, owe their delicacy chiefly to the fact that they precipitate other substances than serumalbumin and are therefore unreliable. All tests containing mercury, tannin, or other strong vegetable acids are fallacious on this account.

Quantitative Determination.—*The gravimetric method* is the most accurate means of determining the quantity of albumin. A mixture of equal parts of a saturated potassium-ferrocyanide solution and acetic acid is added drop by drop to 100 c.c. of the urine until all the albumin has been precipitated. The fluid is then passed through a filter of known weight, the precipitate is washed on the filter with distilled water, alcohol, and ether in succession, and dried at 120 ° C. The filter with its contained albumin is then weighed and the weight of the filter is deducted to give the weight of albumin in 100 c.c. of the urine.

Esbach's Method.—This method is simpler than the preceding, the percentage being measured in a graduated glass tube after precipitation with picric acid. The standard solution is prepared by dissolving picric acid 10 gm., and citric acid 20 gm. in 1,000 c.c. of distilled water. The tube is filled to the mark U with urine, and enough of the reagent is added to raise the level to the mark R (Fig. 49). The tube is then closed with the stopper, inverted several times to mix the fluids thoroughly, and is set aside for twenty-four hours. The degree on the scale corresponding to the level of the precipitate

indicates the number of grams of albumin in a litre of the urine, one-tenth of which number represents the percentage. The figure 7, for example, denotes 7 gm. of albumin to a litre, or 0.7 per cent. If the quantity of albumin be found to be great, the urine should be diluted with one or two volumes of distilled water before the test is made and the result multiplied by 2 or 3 as the volume was doubled or trebled. The fact that picric acid precipitates also mucin, peptone, and the proteoses renders this method liable to frequent error. Uncertainty may result also from a failure of the coagulated albumin to settle completely.

Fig. 49.—Esbach's Albuminometer.

The Centrifugal Method.—This is the quickest method and is even more accurate than that of Esbach. The graduated tube of the centrifuge is filled to the 10 c.c. mark and 3.5 c.c. of a ten-per-cent. potassium-ferrocyanide solution and 1.5 c.c. of acetic acid are added and the fluids are thoroughly mixed. The centrifuge is then revolved until the albumin is all settled, leaving the fluid perfectly clear; each tenth cubic centimetre of the scale represents one per cent. of albumin by bulk.

Care must be taken in all these methods not to confound the real percentage with the apparent percentage by bulk. When the addition of a reagent causes a precipitation which apparently amounts to half the bulk of the fluid, the real percentage is by no means fifty, but may be as low as two per cent.

Globulin.

Globulin (serumglobulin or paraglobin) is usually present in albuminous urine, and, owing to its greater diffusibility, may even exceed the albumin in quantity, although it is less abundant in the blood. The clinical significance of globulin is nearly the same as that of albumin, except that it occurs more frequently, as an accompaniment of albumin, in acute parenchymatous nephritis and in amyloid degeneration of the kidneys. In chronic nephritis it is usually absent or present in only very small amount. Globulin is insoluble in water, but becomes soluble on the addition of an acid or an alkali, and is again precipitated by neutralizing the solution, or by applying heat. Carbon dioxide precipitates it from a faintly alkaline solution, but redissolves it when added in excess. In neutral solutions it is precipitated by the addition of sodium chloride or magnesium sulphate to saturation, and an instance has been reported in which spontaneous crystallization occurred.

Tests for Globulin.

Exactly neutralize the urine and filter, then add magnesium sulphate until it will no longer dissolve. If globulin is present, a white precipitate is formed.

If serumalbumin be also present, it may be detected after filtering the specimen obtained in this test, then adding a few drops of acetic acid and applying heat to boiling.

Daiber, of Zurich, has recently described a method of separating globulin from urine containing also albumin. The method consists in first removing the albumin with alcohol and filtration, washing the precipitate with tepid distilled water, redissolving it with dilute acetic acid, freeing the solution from coloring matter with animal charcoal if necessary, rendering the filtrate neutral or slightly alkaline with sodium-carbonate solution, then adding two parts of a saturated solution of ammonium sulphate. The globulin is precipitated in a flaky deposit, which may be redissolved in a one-per-cent. sodium-chloride solution and precipitated by heat.

Roberts has given us an ingenious test, depending upon the fact that globulin falls out of solution when the specific gravity is reduced to 1.002. A wineglass or test tube is filled with distilled water and the urine is let fall into it in drops. If globulin is present, each drop is followed by a milky streak as it sinks through the water; finally, if sufficient urine be added, the water becomes pervaded by a milky opalescence which is removed by acetic acid.

Proteoses.

Proteoses, intermediate products in the hydration of proteids, are formed within the body by the action of the gastric and pancreatic juices, and are known as albumoses, globuloses, vitelloses, caseoses, or myosinoses, according to the proteid from which they are derived. There are at least three albumoses: protalbumose, heteroalbumose, and deuteroalbumose. These closely resemble one another, are all soluble in dilute solutions of sodium chloride and all yield a red color to the biuret test. Protalbumose and heteroalbumose are primary albumoses, while deuteroalbumose is an intermediate product in the conversion of the primary albumoses into peptone.

Protalbumose is soluble in water and in saline solutions, and is precipitated by saturation with sodium chloride or magnesium sulphate. *Heteroalbumose* is insoluble in water, is soluble in weak saline solutions, but is precipitated by heat (65° C.) from the saline solution, the precipitate being soluble in dilute acids and alkalies; it

may be precipitated also by saturating with the salines, or by a removal of these salts by dialysis, from their solutions. When precipitated by alcohol, a part is converted into insoluble dysalbumose.

Deuteroalbumose, or hydrated albumin, is soluble in water and in ten-per-cent. salt solution, is precipitated from solution by treatment with strong ammonium-sulphate solution, but not by sodium chloride, magnesium sulphate, or cupric sulphate, and yields the characteristic albumose reaction with nitric acid only in the presence of an excess of salt. It therefore resembles peptone more closely than does any of the other albumoses.

The albumoses have been recognized in a great number of diseases, particularly in the infections, in osteomalacia, carcinoma, tertiary syphilis, diphtheria, and hemiplegia.

Peptone.

Peptones, the final products of peptic and pancreatic digestion of proteids, probably appear in the urine only when a peptone is present in the blood as a result of retrogressive changes in the albuminoids of the body or in the corpuscles of the blood, but some observers doubt that true peptone has ever appeared in the urine.

The peptones are described as of two kinds: hemipeptone, which the pancreatic juice converts into leucin, tyrosin, and the like, and antipeptone, which is not thus affected by the pancreatic juice, does not respond to Millon's reagent, or yield tyrosin when treated with sulphuric acid. Peptones are soluble in water, acids, alkalies, and in solutions of ammonium sulphate and other salts; they pass freely through animal membranes by dialysis; they are not precipitated by heat, nitric acid, copper sulphate, potassium ferrocyanide, but are precipitated by tannic acid, picric acid, mercuric chloride, and potassium-mercuric iodide.

Peptonuria is supposed to occur physiologically during the period of involution of the puerperal uterus, and has been described in association with a large number of pathological conditions, particularly in such as denote a destructive metamorphosis of tissue, as in phosphorus poisoning, in suppurative diseases, in nearly all the acute and chronic infectious diseases, in cancer, especially of the stomach, intestines, or liver, in apoplexy, etc., but many early observations have no doubt been erroneous. It has been found occurring periodically in some of these conditions. The occurrence of peptonuria in inflammatory affections is believed frequently to denote the supervention of suppuration, and, according to v. Jaksch, may serve to differentiate cerebrospinal meningitis from tuberculous meningitis, being

present only in the former. Harris, one of the most recent writers on the subject, believes (*American Journal of the Medical Sciences*, May, 1896, p. 557) that nearly all observations on peptonuria have referred in reality to albumosuria, and that the latter term should be substituted for the former. He attributes the presence of albumoses in the urine to the digestive or peptonizing action of microbes on the albumins of the body, an action common to all forms of living organisms, and concludes that "albumosuria may be present in any condition or disease due to the action of micro-organisms within the body, and is thus simply indicative of an infective condition."

Test for Peptone.

Acidulate the urine with acetic acid, saturate with ammonium sulphate, and filter to remove possible albumin, globulin, or albumoses. Then add picric acid or potassium-mercuric iodide; any precipitate resulting is supposed to be peptone. The method of differentiating peptone from its analogue, deuteroalbumose, is found in their different reactions to ammonium sulphate and nitric acid. Peptone gives no precipitate with ammonium sulphate, while deuteroalbumose is precipitated by saturation with it; peptone yields no precipitate with nitric acid, deuteroalbumose yields a precipitate in the presence of a large amount of sodium chloride, the precipitate dissolving on the application of heat and reappearing on cooling.

Serumalbumin, serumglobulin, heteroalbumose, deuteroalbumose, and peptone are all sometimes, although not often, present in the urine at the same time. The best differential test, according to Purdy, is that of Halliburton, which is as follows ("Practical Uranalysis and Urinary Diagnosis," second edition, p. 91):

"1. If the urine give no precipitate on boiling after acidulation, albumin and globulin are absent. If a precipitate occur, albumin or globulin, or both, are present.

"2. If the urine after neutralization give no precipitate on saturation with magnesium sulphate, globulin and heteroproteose are absent. If such precipitate occur, one or the other is present.

"3. If the urine be saturated with ammonium sulphate and filtered, and the filtrate gives no xanthoproteic or biuret reaction (a large excess of potash must always be added), peptone is absent.

"4. If the urine give no precipitate on boiling after acidulation, no precipitate with nitric acid, and no precipitate on adding ammonium sulphate to saturation, peptone can be the only proteid present. Confirm this by the biuret reaction.

"5. If all proteids are present, they may be separated as follows:

Saturate the urine (faintly acidified with acetic acid) with ammonium sulphate. A precipitate is produced. Filter.

(*a*) Precipitate.	(*b*) Filtrate.
Contains albumin, globulin, hetero- and deuteroproteose.	Contains peptone.

"Collect the precipitate on a filter, wash it with saturated solution of ammonium sulphate, and redissolve it by adding a small quantity of water. To this solution add ten times its volume of alcohol; a precipitate is formed; collect this and let it stand in absolute alcohol for from seven to fourteen days. Then filter off the alcohol, dry the precipitate at 40° C., extract with water, and filter. An insoluble residue is left.

(*a*) Residue.	(*b*) Extract.
This consists of albumin globulin coagulated by alcohol.	This consists of the proteoses in solution.

"Heteroproteose is precipitated by heating the solution to 65° C., or by saturating a portion of the extract with magnesium sulphate. Deuteroproteose remains in solution.

"Take another portion of the urine, neutralize it and saturate with magnesium sulphate. A precipitate is produced. Filter.

(*a*) Precipitate.	(*b*) Filtrate.
This consists of globulin and heteroproteose, which may be separated by the prolonged use of alcohol, as above.	This contains albumin, deuteroproteose, and peptone. Add alcohol, as above; albumin is rendered, in seven days, insoluble in water. The deuteroproteose and peptone are soluble, and may then be separated by ammonium sulphate."

Hæmoglobin.

Hæmoglobin, the red coloring matter of the blood corpuscles, is a crystalline, non-diffusible proteid containing iron. It may appear in the urine with or without the accompaniment of blood corpuscles. When it appears without corpuscles, it is as a result of the destruction of the corpuscles within the blood-vessels, as sometimes results from extensive burns, poisoning by phosphorus, by hydrochloric, sulphuric, carbolic, or pyrogallic acid, by potassium chlorate, arseniuretted hydrogen, or by the injection of water, glycerin, or the

blood of another animal into the circulation. It has been attributed to the ingestion of large doses of quinine, and is a well-known result of malarial infection. It is sometimes seen in pyæmia, typhus fever, scurvy, fat embolism, and purpura. Paroxysmal hæmoglobinuria is a condition more frequent in women than in men, sometimes occurring without other apparent cause than exposure or overexertion. It is also a possible accompaniment of Raynaud's disease.

Tests for Hæmoglobin.

1. *The Guaiacum Test.*—If the urine to be tested be alkaline, it must be rendered faintly acid. Equal parts of a freshly prepared tincture of guaiacum and an ethereal solution of hydrogen peroxide, or of ozonized turpentine (turpentine which has stood for a long time exposed to the light and air) are mixed in a test tube—the mixture must not have a blue color. Over this mixture, flow the urine. If hæmoglobin be present, a bluish-green color is produced at the point of contact, changing into a beautiful blue. On shaking, the blue color extends to the entire mixture. The presence of pus also produces a blue color, but this color disappears on boiling the mixture, and it will be found that the reaction occurs with the guaiacum alone.

2. *Heller's Test.*—Render the urine strongly alkaline by the addition of sodium hydrate and heat to boiling. The precipitate of earthy phosphates will be colored red by hæmatin. If only a very small quantity of blood be present, the precipitate thus produced will be dichromic.

If the urine be alkaline in reaction and no precipitate is produced by warming with sodium hydrate, the earthy phosphates having been previously precipitated, the addition of a few drops of magnesium solution will produce an artificial precipitate which, on being warmed, will bring down the hæmoglobin.

3. *The Hæmin Test.*—Filter the urine containing the precipitate produced in the last test, remove some of the precipitate to a microscopic slide, and carefully evaporate it to dryness. Crush and rub into this dry mass one or two small crystals of common salt, add a drop of glacial acetic acid, cover with a glass circle, and warm gently until small bubbles begin to appear under the cover. After cooling, hæmin crystals may be seen with the microscope (Fig. 50).

Fig. 50.—Hæmin Crystals.

4. *Spectroscopic Examination.*—Hæmoglobin may be found in the urine in either of its three forms, but particularly as hæmoglobin or methæmoglobin, since hæmoglobin in acid urine changes to methæ-

moglobin, returning again to hæmoglobin as alkaline fermentation becomes established. Oxyhæmoglobin is produced by exposure to the air. In the spectrum of hæmoglobin, we have a broad band between *D* and *E*, not reaching quite to *E*. Oxyhæmoglobin yields two bands, one yellow, the other green, between *D* and *E*. The latter spectrum may be converted into the former by the addition of a little ammonium sulphide to the solution, thus reducing the oxyhæmoglobin. Methæmoglobin gives a well-defined red line between *C* and *D* (see Fig. 37, p. 280).

Fibrin.

Fibrin, a body which is formed whenever blood, lymph, or transudations undergo spontaneous coagulation, may appear in the urine either in solution or in flakes or in masses of coagula. When very abundant, as it may become in chyluria, fibrin leads to a complete spontaneous coagulation of the urine after it has been voided. In smaller, yet considerable quantity, as occurs in severe inflammatory conditions of the kidney or lower urinary passages, particularly in tumor of the bladder, only a thick, jelly-like, ropy substance appears in the urine.

Tests for Fibrin.

1. Fibrin is not dissolved in water, swells up on the addition of hydrochloric acid, and is dissolved by the addition of pepsin to the acid fluid, with the aid of moderate heat.

2. Separate some of the gelatinous substance by filtration through fine muslin. A dilute solution of sodium hydroxid fails to dissolve it, if it be fibrin. Another portion will completely dissolve in a one-per-cent. solution of sodium carbonate if warmed gently for several hours on a water-bath. Filter this solution and treat with Millon's reagent, and a deep red color will be produced.

Hæmatoporphyrin.

The appearance of hæmatoporphyrin (an iron-free hæmatin) in the urine has been described as found only in women and for the most part in those who have more or less continuously taken sulphonal. It has since been observed, however, in acute lead poisoning and in a number of other conditions, even in healthy men and women. Apparently one of the most logical explanations of its occurrence is given by Stockvis, of Amsterdam (*Zeitschrift für klinische Medicin*, Bd. XXVIII., Hefte 1 und 2), who attributes it to the action of acids on blood which has been effused into the alimentary tract,

as a result of sulphonal or other poisoning. He succeeded in producing hæmatoporphyrinuria in starving rabbits by feeding them with beef or beef blood. The phenomenon does not occur, however, as might be inferred, in all cases of intestinal hemorrhages. MacMunn classes urohæmatoporphyrin among the coloring matters.

The occurrence of hæmatorporphyrinuria is sometimes associated with extreme, even fatal exhaustion. Fatal cases, according to Priestley, have occurred only in women of neurotic type. When the condition has once been established by the administration of sulphonal, it does not always cease upon the withdrawal of the drug. Stern has described the lesions of the kidneys in a fatal case as toxic nephritis with necrosis of the epithelium and hemorrhages into the kidneys. The urine is strongly acid and of a port-wine color, giving a red stain to linen.

The formula for hæmatoporphyrin is believed to be $C_{16}H_{18}N_2O_3$. It is similar to the urospectrin of Saillet.

Test.

To 30 c.c. of urine an alkaline solution of barium chloride is added. The precipitate is washed with water and absolute alcohol and extracted with ordinary alcohol acidulated with hydrochloric acid. The solution has a reddish color if hæmatoporphyrin be present, and its filtrate gives a characteristic, four-banded spectrum, at first sight not unlike hæmoglobin, but undergoing no change on the addition of such reducing agents as ammonium sulphide. One band in the spectrum extends beyond *D* into the red, another lies between *b* and *F*, a third between *C* and *D*, and a fourth between *D* and *E*, nearer *E*. It has further been noted in the cases of Rankin and Pardington (*Lancet*, January 24th, 1891, p. 196) that the addition of strong sulphuric acid brought out a change of color, while the spectroscope showed that the substance has become changed into acid hæmatoporphyrin. Neither hæmoglobin, bile pigment, albumin, nor sugar was present. The odor of the urine was that of acetone, and no decomposition occurred during several months.

Mucin.

Mucin is believed by some observers to be present in small quantity in normal urine (see p. 696), and is doubtless often mistaken for albumin. When abundant, it appears as a ropy, tenacious mass, resembling fibrin. This occurs for the most part in severe cystitis and pyelitis. In febrile states, an increase of mucin frequently precedes the appearance of albuminuria.

Mucin is soluble in alkalies and strong mineral acids, but is pre-

cipitated by dilute mineral acids, strong alcohol, and organic acids and is not dissolved by an excess of acetic acid; it is not coagulated by heat.

Tests.

1. Dilute the urine with an equal volume of distilled water to prevent precipitation of urates and lessen the tendency of the chlorides to hold the mucin in solution; then add an excess of acetic acid. The resulting precipitate is mucin.

2. To differentiate between mucin and albumin, first apply the potassium-ferrocyanide test, and if no precipitation occur test by the preceding method.

Carbohydrates.

This name has been given to a large number of substances which contain carbon, with hydrogen and oxygen in the ratio in which they exist in water. The more commonly encountered carbohydrates contain six atoms of carbon, or a multiple of six, in the molecule. They are neutral in reaction, slow to enter into composition, and, with the exception of inosite, possess a rotatory power over polarized light. Grape sugar (glucose or dextrose), lævulose, lactose, and inosite are the carbohydrates most frequently found in the urine.

Glucose.

Grape sugar ($C_6H_{12}O_6$) probably exists in minute quantity in normal urine, but must be considered abnormal when found in sufficient quantity to yield a reaction with the tests ordinarily employed for its detection. Von Noorden expresses doubt whether the slight traces of sugar which are found in normal urine pass through the epithelium of the glomeruli with the aqueous portion of the urine, and suggests that they may originate from destroyed epithelial nuclei, or from mucin, since Kossel has demonstrated that a carbohydrate can be formed by the decomposition of nucleoalbumin or nuclein, and it has been long known that mucin contains a detachable molecule of carbon hydrate.

Clinical Significance.—Glycosuria is the cardinal symptom of diabetes mellitus, but it may occur as a transitory condition, or more permanently in old age, in obesity, intermittent fever, scarlatina, cerebrospinal meningitis, cholera, gout, and in diseases of the lungs, liver, pancreas, or brain, particularly in lesions located in the vicinity of the fourth ventricle. It is sometimes found in nervous conditions, as neuræsthenia, and in recent cases of insanity, particularly in melancholia.

The administration of certain medicines is said sometimes to produce glycosuria; it at least produces a condition of the urine which causes a reduction of copper. This is claimed for curare, carbonic oxide, amyl nitrite, methyl delphinin, morphine, chloral, tannic acid, hydrocyanic acid, turpentine, uranium nitrite, phenol, benzol, acetone, phloridzin, and thyroid extract after continued use. If sugar be ingested in quantity beyond the ability of the individual to assimilate it, a portion of it will be carried off in the urine. It does not necessarily appear as glucose, however, but as the kind of sugar which has been administered. Von Noorden places the normal limit of assimilation by a healthy person at from 200 to 250 gm. of grape sugar, 200 gm. of fruit sugar, 150 to 200 gm. of cane sugar, and 120 gm. of milk sugar. The name *alimentary glycosuria* has been given to the appearance of sugar in the urine thus produced, and v. Jaksch has applied this method of producing it as a test, administering 100 gm. of grape sugar; if a portion of it appears in the urine, he considers it an evidence of incipient diabetes, or at least of a tendency to the disease; but the test has been found to react also in some cases of cerebral disease, in hysteria, pregnancy, atrophic cirrhosis, and phosphorus poisoning.

Normal urine contains other substances, however, than sugar, which are known collectively as "reducing agents," which are capable of causing a variable degree of reduction of cupric sulphate in the presence of an alkali. Chief among these substances are uric acid, creatinin, the coloring matters of urine, and the bile pigments. And, on the other hand, diabetic urine sometimes undergoes a change on standing by which urea is split up into ammonia and carbonic acid, in quantity sufficient to impair the accuracy of the sugar tests.

Tests for Sugar.

Detection.—1. *Trommer's Test.*—Several methods of securing Trommer's reaction are in use. The older method is as follows: (*a*) To a small quantity of urine in a test tube add half as much liquor potassæ (1:3), and to this add, drop by drop, a solution of cupric sulphate (1:10), shaking after each addition, until a clear, azure blue color is produced; then heat the mixture to boiling. If sugar be present, a reduction of the copper to cuprous hydroxide at once begins, the color changing first to yellow, and finally to a red cuprous oxide.

(*b*) To about a drachm of the urine in a test tube add enough cupric sulphate solution to produce a light green color; then add an equal volume of potassium, or sodium hydroxide solution, and shake well. The color changes to a deep blue, particularly if sugar be pres-

ent. The reduction is now brought about by the application of gentle heat. Boiling is unnecessary and is liable to produce reduction from the presence of such other substances as uric acid, hippuric acid, carbolic acid, tannic acid, or hypoxanthin, certain alkaloids, or glycuronic acid. Salkowski recommends the use of a method practically the same as the last, using sodium hydroxide solution of thirty-three per cent.

2. *Fehling's Test.*—The reagents employed for this test are as follows:

(*a*) Copper Solution: Dissolve of pure crystallized cupric sulphate 34.64 gm. in enough distilled water to make 500 c.c.

(*b*) Rochelle-Salt Solution: Dissolve sodium hydroxide, 125 gm., and chemically pure potassium-sodium tartrate, 173 gm., in sufficient distilled water to make 500 c.c.

These solutions should be kept separately in well-stoppered bottles; mixture of equal parts of each at the time of using gives Fehling's solution.

For qualitative testing, about 1 c.c. of Fehling's reagent is diluted with three or four times as much distilled water in a test tube and boiled. If no change of color takes place, the urine is added, drop by drop, until a slight reduction of the copper occurs, or until the quantity of added urine equals that of the reagent. The mixture is again heated; if sugar is present, a yellow color appears. If no reduction occurs, the mixture is set aside for several hours, and if no reduction occurs in that time, sugar is not present.

This test is one of the most delicate as well as one of the most reliable of the copper tests. The objection usually made to it, that the solution does not keep, cannot be applied to the method given, as the solutions in separate bottles keep indefinitely. The preliminary boiling of the solution gives ample protection against the reaction of racemic acid, which sometimes results from a decomposition of potassium-sodium-tartrate solution. The test is, nevertheless, open to the objection that many other substances cause a reduction almost identical with that of glucose.

3. *Haines' Test.*—This test is recommended by Purdy as the best copper test for qualitative analysis. The formula is: Copper sulphate thirty grains, distilled water, half an ounce; make a perfect solution and add pure glycerin half an ounce; mix thoroughly and add five ounces of liquor potassæ. Take about one drachm of this solution in a test tube and gently boil it; then add six or eight drachms (not more) of the suspected urine and again gently boil it. If sugar be present, a copious yellow or yellowish-red precipitate is thrown down.

4. *Elliott's Method.*—Dr. A. R. Elliott claims for the following modification of Fehling's solution a greater delicacy than that of Haines' test, as well as permanency of the solutions. The reagents are as follows: (*a*) Pure cupric sulphate, 27 grains; pure glycerin, 3 drachms; distilled water, 2½ drachms; liquor potassæ, enough to make 4 ounces. Dissolve the cupric sulphate in the glycerin and water with the aid of gentle heat; when cold, add the liquor potassæ and mix thoroughly. (*b*) A saturated solution of chemically pure tartaric acid in distilled water.

Into a test tube pour a drachm of the cupric sulphate solution and gently boil. Then add two or three drops—not more—of the tartaric-acid solution and boil again. Now add the urine, drop by drop, boiling and shaking after each addition until reduction takes place or until eight drops of the urine have been added. If no reduction takes place, sugar is not present. The end reaction is a yellowish or reddish, sometimes a greenish-gray deposit.

5. *Böttger's Bismuth Test.*—Add to the urine an equal volume of potassium hydroxide solution and a little pure bismuth subnitrate, then boil gently for from one to two minutes. If sugar be present, the mixture turns gray or black, according to the quantity present. If the quantity be very small the bismuth alone may become darkened, and for this reason only a fraction of a grain of bismuth should be used, since the reaction is more readily detected. Albumin, or other body containing sulphur, will produce the reaction and must first be removed. (Never make this or other bismuth test in a tube which has been used for a copper test.)

6. *Nylander's Test.*—The solution used in this test is made by dissolving bismuth subnitrate, 2 gm.; sodium-potassium tartrate, 4 gm.; and sodium hydroxide, 8 gm., in 100 c.c. of distilled water, gradually added with stirring. After the solution is complete, filter. Add 1 c.c. of this solution to 10 c.c. of urine and boil for two minutes in a long test tube. If sugar be present, a gray or black precipitate forms. Albumin must not be present.

7. *Phenylhydrazin Test.*—This test is of great value, since it gives no reaction with a large number of substances which cause reduction of the copper reagents. To 25 c.c. of urine in a capsule add 1 gm. of phenylhydrazin hydrochloride, 0.75 gm. of sodium acetate, and 10 c.c. of distilled water. Warm the mixture on a water-bath for an hour, remove, and let it cool. If sugar be present a yellowish deposit is formed which the microscope shows to consist of fine, brilliant yellow crystals, arranged singly or in stars, of phenylglucosazone, the melting point of which is 204° C. (Fig. 51). Yellow scales or powerfully refracting spheres do not denote the presence of sugar. (Care

must be taken not to permit the phenylhydrazin to come into contact with the fingers.)

8. *The Fermentation Test.*—This test is one of the most positive in its results, and is generally used to confirm the results of other tests. It depends upon the fact that glucose is acted upon by the yeast plant to form alcohol, liberating carbon dioxide.

The simplest accurate method of performing the test is by filling a test tube about half-full of mercury, completely filling the remainder of the tube with the urine to be tested, introducing a small piece of compressed yeast and inverting the tube over a vessel of mercury. Set the tube in a warm place for several hours. If fermentation

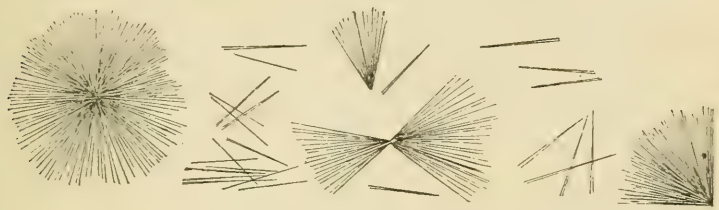

Fig. 51.—Rosette and Rays of Phenylglucosazone Crystals.

occurs, the carbonic-acid gas will collect in the upper end of the tube. A special apparatus may be purchased, or may be easily made by passing a doubly bent tube through a cork nearly to the bottom of a bottle containing the yeast and urine, hermetically sealing the cork. If fermentation occur, the fluid is expelled through the tube, its place being taken by the liberated carbonic-acid gas. The only precaution usually required in making this test is to perform a control test, using yeast from the same piece in a tube of water, for yeast sometimes undergoes spontaneous fermentation, probably owing to the presence of sugar. If this occurs, a difference in the quantity of gas evolved may be sufficient to indicate the presence of sugar in the urine. If any doubt exist as to the vitality of the yeast, a second control may be made with a weak solution of glucose.

It is not necessary to boil the urine, as recommended by some authors, since it rather increases the liability to error by driving off any contained carbonic-acid gas, for urine is capable of absorbing enough of this gas at all times to impair the accuracy of the fermentation test. About one per cent. of sugar is the least that can be detected by this method. Some writers have claimed much greater delicacy for it, evidently overlooking the fact that an equivalent of about 0.5 per cent. is absorbed by the urine.

9. *The Heller-Moore Test.*—To a little urine in a test tube add half

its volume of sodium or potassium hydroxide solution and heat to boiling; if the precipitation of earthy phosphates is abundant, filter. As the mixture becomes hot, a light yellow, yellowish-brown or brownish-black color appears if sugar be present. Now add a few drops of nitric acid; the color vanishes and an odor of molasses (caramel) is given off. If albumin be present, it must be removed by boiling and filtration before this test is applied. If the urine is highly colored, as is rarely the case with saccharine urine, it should be decolorized by filtration through animal charcoal or by treatment with acetate of lead. Some sugar is removed, however, by this means.

10. *Mulder's Indigo-Carmine Test.*—Heat a solution of indigo carmine, rendered alkaline with sodium carbonate, in a test tube, and while hot add a few drops of the urine; a series of colors, terminating in yellow, will be produced if sugar be present. This test is conveniently made with test papers or compressed tablets.

11. *Picric-Acid Test.*—To a small quantity of urine in a test tube add two-thirds its volume of a saturated solution of picric acid and as much liquor potassæ. An orange color results from the incipient reducing action of creatinin on the picric acid. Turbidity denotes the presence of albumin, but does not interfere with the test. Boil the mixture for one minute; if sugar be present, a deep mahogany-red color is produced, much deeper than that which occurs in normal urine.

Quantitative Determination.—A reliable means of determining the quantity of sugar discharged in the urine of a diabetic patient is important, in that it reveals the severity of the case, modifies its prognosis, and shows the results of treatment.

1. *Fermentation Method.*—This is the simplest and one of the most accurate methods of determining the quantity of sugar in the urine. Roberts has shown that, as a result of fermentation, the urine loses one degree of specific gravity for each grain of sugar in the fluid-ounce. Three or four ounces of urine in which sugar has been detected are placed in a convenient bottle and a little compressed yeast is added; the mouth of the bottle is closed by a loose stopper or wad of absorbent cotton. The bottle is then set aside in a warm place for about twenty-four hours to ferment. Another bottle of the urine, free from yeast, should be set aside with it, in order to avoid errors due to temperature, in comparing the specific gravity. When fermentation has ceased, decant the urine and take its specific gravity and that of the unfermented urine; the difference in degrees will represent the quantity of sugar in each ounce of the urine, a loss of twenty degrees of density indicating twenty grains of sugar in an

ounce of the urine. The percentage may be approximately obtained by multiplying this number by 0.23.

Einhorn's saccharimeter is an instrument for estimating the quantity of sugar from the volume of carbonic acid evolved in the fermentation. Unfortunately, no allowance is made for the quantity of gas absorbed by the urine, which is always sufficient to render the result inaccurate. The urine is said to absorb a volume of the gas equal to its own.

2. *Fehling's Method.*—The standard solution for quantitative analysis is thus prepared: Pure crystallized cupric sulphate, 34.639 gm.; solution of sodium hydroxide (of specific gravity 1.12), about 500 c.c.; chemically pure neutral sodium tartrate, 173 gm. Dissolve the cupric sulphate in 100 c.c. of distilled water. Dissolve the sodium tartrate in the sodium-hydroxide solution and add the copper solution very slowly; then add sufficient distilled water to make the solution measure 1,000 c.c. The estimation of sugar by this method depends upon the fact that 0.05 gm. of sugar is required to reduce 10 c.c. of the standard solution.

Ten cubic centimetres of the standard Fehling's solution are placed in a flask and diluted with three or four volumes of distilled water. The urine to be tested is diluted to a definite number of times its volume with distilled water, usually to ten volumes, unless the quantity of sugar be very small, when dilution to five volumes is sufficient. A burette is now filled with the diluted urine; the Fehling's solution in the flask is heated to boiling and the urine is added in successive small quantities until the blue color has entirely disappeared. The mixture must be boiled and allowed to settle for a few minutes after each addition of the urine, in order that any blue color remaining may be recognized. When the blue color has disappeared, the quantity of diluted urine that has been used is read from the burette scale and the calculation is made. If, for example, 10 c.c. of the diluted urine (representing 1 c.c. of the urine) were required to reduce 10 c.c. of the Fehling's solution, 100 c.c. of the urine would contain 5 gm. of sugar, or five per cent.

3. *Pavy's Modification.*—Pavy improved the Fehling's solution by adding ammonia to the formula, rendering the determination of the end result much easier; but since the chief objection to the Fehling method lies in the instability of the sodium tartrate, his method is still open to objection.

The standard solution is prepared by dissolving 20.4 gm. each of potassium-sodium tartrate and potassium hydroxide in about 100 c.c. of distilled water, and 4.158 gm. of cupric sulphate in a like quantity of water, with the aid of heat, and pouring the latter solution into the

former. When cold, 300 c.c. of ammonia (specific gravity, 0.88) are added, and sufficient water to make 1,000 c.c. The method of titration is practically the same as that just described; each cubic centimetre of the reagent representing 5 mgm. of sugar.

4. *Purdy's Method.*—Purdy has undoubtedly given us the best modification of the Fehling method that has yet been proposed, in that he makes use of Pavy's improvement by the addition of ammonia and avoids the use of the unstable sodium tartrate. Its advantages are thus stated by the author, "1. Its perfect end reaction, whereby even the inexperienced observer may accurately determine the precise point of complete reduction without delay. 2. Its stability, which is such that the solution may be kept on hand for months without impairment of its qualities for testing. 3. Its rapidity of application, by means of which one is enabled to determine the quantity of sugar in a given sample of urine within five minutes. 4. Its accuracy, which any one may readily prove by submitting it to solutions of grape sugar in normal urine of known and accurately measured strength. 5. Its simplicity, the apparatus required being of the most common order."

The formula for Purdy's standard solution is: Cupric sulphate (C. P.), 4.742 gm.; potassium hydroxide (caustic potash) (C.P.), 23.50 gm.; strong ammonia (U. S. Ph.) (specific gravity, 0.9), 450 c.c.; glycerin (C.P.), 38 c.c.; distilled water, to make 1,000 c.c. Dissolve the cupric sulphate and glycerin in 200 c.c. of distilled water, with the aid of gentle heat. In another 200 c.c. of distilled water, dissolve the potassium hydrate. Mix the two solutions and, when cold, add the ammonia. Finally, with distilled water, bring the volume of the whole to exactly 1,000 c.c. Thirty-five c.c. of this solution are reduced, upon boiling, by exactly 2 cgm. (0.02) of grape sugar. The analysis requires a glass flask of 150 to 200 c.c. capacity, a common retort stand, a 10 or a 20 c.c. graduated burette, and a large spirit lamp. Proceed as follows:

Measure exactly 35 c.c. of the test solution into the flask, dilute it with about two volumes of distilled water, and bring the whole thoroughly to the boiling point. Fill the burette to the zero mark with the urine to be tested, and slowly discharge the urine into the test solution, drop by drop, until the blue color begins to fade, then *still more slowly* (three to five seconds elapsing after each drop), until the blue color completely disappears and leaves the test solution perfectly transparent and colorless. (A return of the blue color after standing some time is due to the absorption of oxygen from the air and has no bearing on the test.) The percentage table of results is as follows: If the 35 c.c. of test solution were reduced by 2 c.c. of

urine, the latter contained exactly 1 per cent. of sugar; if reduced by 1 c.c., 2 per cent. of sugar; if by 0.75 c.c., 3 per cent.; if by 0.5 c.c., 4 per cent.; if by 0.25 c.c., 8 per cent. The accurate application of the test is less difficult, if the urine be diluted with two volumes of water, and the result multiplied by 3, unless the percentage of sugar is very low.

5. *Polariscopic Method.*—The polariscope probably affords the most accurate means of determining the percentage of sugar in the urine, providing the quantity exceeds one per cent. Unfortunately the instrument is an expensive one and requires some practice before satisfactory results can be obtained from it. Its use depends upon the fact that glucose has a dextrorotatory power over light, the degree of rotation corresponding to the quantity of sugar present in the solution through which the light is passed. If the urine contain albumin, this must be removed; if it be high-colored, it must be clarified by passage through animal charcoal, or by precipitation with basic lead acetate (1:10).

To use the instrument, the tube is filled with urine and it is set in position between the polarizer and the analyzer. The polarizer is then so adjusted by means of a screw that both sides of the field are equally illuminated. The degree of rotation produced by the passage of the light through the solution is measured on a scale, from which the quantity of sugar present is calculated. On some polariscopes (as the Soleil-Ventzke) the scale is made to indicate percentages, on others a calculation must be made. In Laurent's polariscope, probably the best instrument, the number of degrees of dextrorotation must be multiplied by 0.2051 to ascertain the percentage of glucose.

Ultzmann has devised a polariscope which can be adjusted to the stand of a microscope after removal of the ocular and objective. It possesses nearly all the advantages of the larger instrument and is much cheaper.

Cane sugar and milk sugar cause dextrorotation also. The degrees of rotation are, for glucose +53.1°, for lactose +59.3°, and for cane sugar +73.8°. Levulose and albumin rotate the rays of light to the left. The presence of albumin reduces the degree of dextrorotation produced by glucose; it should be removed by ten-per-cent. lead-acetate solution. Hydroxybutyric acid may also cause confusion (see p. 744).

Inosite.

Inosite ($C_6H_{12}O_6$), or muscle sugar, is a crystalline body forming large, colorless, monobasic, efflorescent prisms, soluble in warm

water, insoluble in alcohol and ether. Although chemically identical with grape sugar, it does not reduce copper sulphate in the presence of an alkali, giving only a greenish color on boiling with the copper reagents, the color vanishing on cooling to reappear on boiling; it does not undergo alcoholic fermentation and causes no rotation of polarized light.

Clinical Significance.—Inosituria is frequently associated with glycosuria in diabetes and occasionally accompanies albuminuria. It has been observed also in typhus, tuberculosis, and syphilis, and, according to Ralfe, as an independent affection, characterized by malaise, aching of the limbs, and moderate polyuria.

Tests.

1. Evaporate the solution containing inosite with a little nitric acid on platinum almost to dryness, add a little ammonia and calcium chloride solution, and again evaporate carefully to dryness; a brilliant rose-red or violet color will be produced. Other sugars do not give this reaction.

2. The following solution must be prepared: Dissolve one part of mercury in two parts of nitric acid, evaporate to one-half its volume, and add one and one-half parts of distilled water. Allow this to stand for twenty-four hours and pour the clear fluid from the salt. If a little of this solution be added to a solution containing inosite on a porcelain dish, a yellow precipitate is formed; and if this be heated, it becomes red, the color vanishing on cooling, to return on being reheated. Albumin gives a red color with this test, and should therefore be first removed; grape sugar gives a black color reaction. Few, if any, other substances react in a way to cause error with this test.

3. Inosite may be obtained from the urine in the following manner: All albumin that may be present is first removed; the urine is then treated with neutral plumbic acetate so long as a precipitate is produced. It is then filtered and the filtrate is treated with subacetate-of-lead solution until precipitation ceases. It is recommended to concentrate the urine to one-fourth its volume before precipitation. After twelve hours the lead precipitate is collected, washed, suspended in water, and decomposed with hydrogen sulphide. After standing a while, a little uric acid separates and should be removed by filtration. The filtrate is then concentrated by boiling and treated, while boiling, with three or four times its volume of alcohol. If the resultant precipitate be heavy and adherent to the glass, the alcohol is poured off; if it be non-adherent, it is separated by filtration through a heated funnel and allowed to cool. If after twenty-four

hours inosite crystals appear, they are separated by filtration and washed with a little cold alcohol. If no crystals appear, ether is added to an alcoholic filtrate until a milky cloudiness results after standing, and this is allowed to stand in a cold place for twenty-four hours. Nearly all the inosite will be thus separated in shining, pearly leaflets, unless too little ether has been used.

Lactose.

Lactose, or milk sugar ($C_{12}H_{22}O_{11}$), crystallizes in white, rhombic prisms, soluble in six parts of cold water or in two and one-half parts of hot water, but insoluble in ether or alcohol. In aqueous solution it possesses dextrorotatory power of 59.3°, and reduces copper salts on boiling in alkaline solution, but it does not readily undergo alcoholic fermentation. After prolonged boiling with dilute acids it forms galactose, which, when treated with nitric acid, yields mucic acid.

Lactose sometimes occurs in small quantity in the urine of nursing women; it is generally present in the urine two or three days after confinement, just before mammary secretion becomes established, and again a day or two after weaning. Inflammation of the mammary glands, by preventing the escape of milk, may produce lactosuria.

Test.

If it be found, under the circumstances just referred to, that the urine reacts to the sugar tests, and at the same time produces strong dextrorotation of light, lactose is probably present. This may be confirmed, first, in a measure, by the tardy action of the fermentation test or by its failure, and second, by treating the urine with lead acetate, filtering, and adding ammonia to the filtrate until a permanent precipitate is produced; then heating the fluid without boiling it, and if a rose-red color, which is characteristic of glucose, does not develop, lactose is present.

Levulose.

Levulose, or fruit sugar ($C_6H_{12}O_6$), is a non-crystallizable body found in the urine, alone or more usually in association with glucose, and attended by the other symptoms of diabetes. It responds to the copper tests for glucose, and yields the characteristic yellow crystals with the phenylhydrazin test, but the crystals melt at 150° C., while those of phenylglucosazone fuse only at 204° C. An aqueous solution of levulose causes rotation of polarized light to the left.

From the fact that dilute mineral acids convert cane sugar into

equal parts of dextrose and levulose, it has been inferred that the latter body may result from an excessive ingestion of cane sugar, as well as from the sugar of fruits, the splitting up of the cane sugar taking place in the intestines.

Test.

If the urine gives the reactions of glucose in the copper and phenylhydrazin tests, but rotates polarized light to the left, levulose is probably present. The difference in the melting point of the crystals may be tested. If albumin and other bodies which rotate light to the left be excluded, the presence of levulose may be considered established.

Cane Sugar.

Saccharose, or cane sugar ($C_{12}H_{12}O_{11}$), is occasionally found in the urine, supposedly as a result of the free ingestion of saccharine matter.

Test.

Cane sugar in solution is strongly dextrorotatory (73.8°), but it does not respond to the copper tests. If, however, a solution of cane sugar be boiled for some time, especially if in the presence of a dilute mineral acid, it becomes converted into dextrose and levulose, both of which substances reduce the copper salts, and cause levorotation of light.

Maltose.

Maltose, which is chemically identical with cane sugar, is possibly at times found in the urine, as in a reported case of atrophy of the pancreas. It, with dextrin, is formed by the action of the diastatic ferment, or by that of dilute acids on starch. Like cane sugar, it is strongly dextrorotatory. With diastase, it is an end product, but by the continued action of the acid it becomes further changed into dextrose. Boiling the urine with sulphuric acid is believed by v. Jaksch to increase its reducing power if maltose be present. With the phenylhydrazin test, crystals are formed (maltosazone) resembling those of glucosazone, but melting at from 190° to 191° C.

Pentose.

Salkowski first called attention to the subject of pentosuria in 1892, and has recently reported three cases in which he made a thorough investigation of it and the means for its detection.

Pentose is a sugar-like carbohydrate, having five atoms of carbon. To the phenylhydrazin test for glucose it yields readily citron-yel-

low crystals whose melting point is 159° C. These phenylpentosazone crystals are soluble in hot water, insoluble or but slightly soluble in cold water, thus differing from phenylglucosazone.

The urine in which pentose was found was invariably of normal yellow color, clear, free from sediment, without albumin or fermentable sugar, and was optically inactive. Upon the application of the ordinary tests for sugar, however, its behavior was such as to excite suspicion of the presence of sugar, although none of the tests produced an altogether typical reaction. Polarization resulted negatively.

Tests.

Salkowski's Method.—Take from 200 to 500 c.c. of urine, and for each 100 c.c. 2.5 gm. of phenylhydrazin (not the hydrochloride). Dissolve the phenylhydrazin in enough acetic acid to give a distinctly acid solution. Add this solution to the urine in a beaker and heat the mixture on a wire net over the flame until it commences to boil. Then place the beaker on a water-bath containing hot water and allow it to remain for from an hour to an hour and a quarter. Remove the beaker, and set it aside until the next day to permit spontaneous crystallization to occur, or this result may be hastened by immersing the beaker in cold water. The hot solution has a brown color and may contain a few brownish flocculent particles, but as crystallization reaches maturity the flask becomes filled with a jelly-like mass of fine yellow needles. If pentose be absent, no crystallization will take place—only a brown granular sediment.

The crystals may now be filtered out, washed with cold water, and partially dried on filter paper, redissolved in hot water, or better, in hot water to which alcohol has been added. Upon cooling this solution, the phenylpentosazone separates in sparkling yellow crystals which when dried will show a melting point at 159° C. If impure, however, they may melt at 156° C.

Tollens' Reaction.—To 5 or 6 c.c. of fuming hydrochloric acid add a few more crystals of phloroglucin than can be dissolved without the aid of heat; divide the solution into two equal parts and allow it to cool. To one portion, in a test tube, add about 0.5 c.c. of the urine, which should be previously concentrated, and to the other portion add a like quantity of normal urine of the same concentration. Then place the tubes in a beaker containing boiling water. If pentose be present, there appears after a few seconds, in the upper stratum of the urine, a deep red color, which gradually extends to the underlying fluid, while the normal urine shows very little or no change of color. The test tubes must be removed from the warm water as soon as the change of color commences, in order to get a pure

reaction and to prevent possible confusion by the action of the hydrochloric acid on glucose, if this be also present.

Clinical Significance.—This has not been positively determined; in fact, pentose cannot be definitely classed as an abnormal constituent of the urine; but Salkowski suggests the propriety of testing for it in all cases of neurasthenia, or whenever the urine is greatly reduced. No definite relation could be determined between pentosuria and glycosuria, but Blumenthal has expressed the opinion that pentosuria may be a forerunner of glycosuria, or that the two conditions may occur alternately in the same subject.

Glycuronic Acid ($C_6H_{10}O_7$).

Glycuronic acid occurs in the urine in combination with potassium under the formula, $C_6H_9KO_7$. Although clearly related to the carbohydrates, particularly to dextrose and inosite, from one or both of which it is probably derived in the organism, it shows also a relation to the aldehyde group by forming a combination with urea to form decomposition products of the aromatic series.

The chief importance of glycuronic acid in urinary analysis lies in the fact that it is of all substances the most likely to be mistaken for glucose, yielding characteristic reactions to the copper, silver, and mercury tests, and rotating polarized light to the right. It occurs in the urine of a healthy person after the administration of such drugs as chloral hydrate, butyl chloral, nitrobenzol, curare, camphor, morphine, and chloroform. This fact is probably the explanation of the belief that the administration of these substances may produce glycosuria, to which reference has been made.

Tests.

If the urine reacts to the copper tests and has the power of dextrorotation of polarized light, but fails to undergo alcoholic fermentation with yeast, the presence of glycuronic acid is indicated.

Schmiedeberg and Mayer have obtained glycuronic acid from the urine by the following method: A large quantity of urine is decolorized with animal charcoal, evaporated to a syrupy consistence, and digested with damp barium hydrate with moderate heat over a water-bath. It is then extracted with absolute alcohol, which leaves the glycuronic acid and other substances undissolved. The residue is then mixed with water and filtered, and barium hydrate is added to the filtrate; it is again filtered and the filtrate is evaporated over a water-bath. A barium compound now separates, which is washed with water and decomposed with sulphuric acid. The barium sulphate is

now removed by filtration; the filtrate is evaporated and dried in vacuo, the resulting crystals being glycuronic anhydride.

Glycogen.

This substance, normally present in the liver, muscles, blood corpuscles, cartilage cells, pus corpuscles, the placenta, and in embryonic tissues, may be detected in the urine in certain diabetic conditions. It is strongly dextrorotatory (= + 211°), but does not react to the copper tests. With iodine it gives a port-wine color which disappears on being heated and returns on cooling.

Acetone.

Acetone (C_3H_6O) is a watery, colorless liquid of ethereal odor, resembling alcohol in specific gravity and boiling at 56.5° C. It may be obtained by distillation from diabetic urine, sometimes from the urine of healthy children.

Pathologically, acetonuria may be produced by excessive ingestion of animal food; it is found in the urine of many diabetics, particularly when the disease is advanced. It may arise from disordered states of the digestive organs and is often associated with malignant disease, especially cancer, or with the state of marasmus following disease, or starvation, or with psychoses. It is quite constantly associated with febrile states independently of any particular infection, but corresponding as a rule to the degree of pyrexia. Becker has found acetonuria of several days' duration coming on several hours after anæsthesia in two-thirds of a large number of cases, and seemingly without relation to the kind of anæsthetic agent that had been employed.

A condition of acetone autointoxication has been described, the manifestations of which were restlessness, even delirium, rarely if ever terminating in coma, but occurring, it might be, as a forerunner of fatal diaceturia.

Tests.

1. *Iodoform Test.*—Ralfe devised the following modification of the Lieben test: Dissolve twenty grains of potassium iodide in a drachm of liquor potassæ and boil. Apply the test by the contact method, gently flowing the urine upon the surface of the solution. At the point of contact a precipitation of phosphates occurs; if acetone be present, this cloud becomes yellow from a studding with minute clusters of iodoform crystals. The test may be used with greater delicacy by first distilling the urine and using the distillate.

2. *Chautard's Test.*—A drop of an aqueous solution of magenta decolorized with sulphuric acid gives a violet color with fluids containing more than 0.01 per cent. of acetone. Five minutes may be required to bring out the reaction in dilute solutions.

3. *Le Noble's Test.*—Prepare a solution of sodium nitroprusside, so dilute as to have only a pale red color (not exceeding one per cent.). To this add an equal volume of the urine and a little ammonia; if acetone be present, a ruby red color is produced, varying in intensity with the quantity of acetone present, and soon changing to yellow, or to a greenish-blue or violet if an acid be added, or if the mixture be boiled.

4. *Baeyer's Test.*—Dissolve a few crystals of meta-nitrobenzaldehyde in the urine, with the aid of heat; on cooling, the aldehyde separates in the form of a white cloud. Add sufficient dilute sodium solution to render the mixture alkaline; if acetone be present, a yellow color appears, changing into green, then into indigo blue within ten minutes.

5. *Reynolds' Test.*—This test is based on the power of acetone to promote solution of mercuric oxide. The method is as follows: Yellow mercuric oxide, freshly precipitated by the reaction between mercuric chloride and an alcoholic potassium-hydroxide solution, is added to a small quantity of the urine, the mixture is shaken and filtered. To the clear filtrate ammonium sulphate is then carefully added; if acetone be present, some of the mercuric oxide has been dissolved and a black ring of mercuric sulphide appears at the plane of contact between the two fluids.

Diacetic Acid.

Diacetic acid, or ethyldiacetic acid ($C_6H_{10}O_3$) is frequently mistaken for acetone. It is a colorless, acid liquid, miscible in all proportions with water, alcohol, and ether. The aqueous solution is decomposed by heat into acetone and carbon dioxide. Under the influence of alkalies, diacetic acid takes up water and splits into acetone, alcohol, and carbon dioxide. With ferric chloride it gives a violet-red or mahogany color, thus differing from acetone; the color markedly decreases in twenty-four hours or upon boiling, thus differing from acetic acid, salicylic acid, antipyrin, phenol, sulphocyanides, and some other substances. It is supposed to originate from the decomposition of sodium diacetate in the blood; Halliburton, however, attributes it to hydroxybutyric acid.

Diaceturia is always pathological and is always of serious moment, but is least serious when it occurs in the febrile conditions of children. In diabetes it occurs especially in young subjects, and at a late

period of the disease. It is usually a precursor or an accompaniment of the fatal coma, if, indeed, the diacetæmia does not induce the coma. It occurs sometimes also at the height of acute fevers, shortly before death.

Diacetæmia, recognized by vomiting, dyspnœa, jactitations, and diaceturia, has been observed as an autointoxication, most cases rapidly passing into a fatal coma without other discoverable disease.

Test.

Von Jaksch's Method.—To some recently voided urine add a few drops of ferric-chloride solution. If the phosphates are precipitated, remove them by filtration, and to the filtrate add a few drops more of the ferric-chloride solution. If a red color is produced boil a portion of the urine, and to another portion add a few drops of sulphuric acid and shake with ether. If diacetic acid be present, the red color will appear but faintly in the boiled portion, it will grow pale in the ethereal mixture during the course of twenty-four hours, and acetone will be found abundant in a distillate of the urine.

Bile.

Either the acids or the coloring matters of the bile may be found in the urine, separately or together.

The Bile Acids.

Although it is probable that exceedingly small traces of the bile acids exist in normal urine (Oliver estimates the quantity as 1 part in from 10,000 to 15,000 parts of urine), it is seldom that they are found in appreciable quantity. Pathologically, however, they may be found associated with the bile coloring matters in conditions attended with icterus, and, according to Oliver, they precede the appearance of the pigments and persist for some time after the latter have disappeared. In the so-called bilious attacks, due, it is supposed, to defective elimination of bile and consequent retention of bile elements in the blood, as indicated by chilliness, headache, pallor, slow respiration, feeble pulse, coldness of the extremities, nausea, vomiting, sometimes diarrhœa—a condition which may deepen into cholæmia, with convulsions, subnormal temperature, albuminuria, hæmoglobinuria—the bile acids are diminished in quantity in the urine, but become increased with the subsidence of the attack.

Among the conditions which are accompanied by an increased excretion of bile acids in the urine are, acute febrile attacks, such

hepatic conditions as congestion, early cirrhosis, amyloid disease, acute yellow atrophy, fatty degeneration due to phosphorus poisoning, carcinoma, and other tumors. It may occur also in malignant disease elsewhere situated, in splenic leucocythæmia, malaria, anæmia, scurvy, chronic interstitial nephritis, and in diseases attended with hæmoglobinuria.

Tests.

Detection. *Pettenkofer Test.*—Concentrated sulphuric acid free from nitric or sulphurous acid, is very slowly added in nearly equal volume to the urine, the test glass being held in ice water to prevent rise of temperature above 60° C. A ten-per-cent. solution of cane sugar is then added, drop by drop, with constant stirring. A beautiful red color indicates the presence of bile acid. This color becomes a bluish-violet during the course of a few days. The liquid, on spectroscopic examination, gives two absorption bands, one at *F*, the other between *D* and *E*, nearer *E*. The chemical test fails if too much sugar has been added, if the temperature has been allowed to rise too high, or if albumin, oleic acid, amyl alcohol, or morphine be present. The spectrum is, however, trustworthy.

It is necessary in most instance, as when the urine is highly colored with bile pigments, to isolate the bile acids before applying Pettenkofer's test. Hoppe-Seyler's method of doing this is as follows: From 100 to 500 c.c. of the urine are evaporated to the consistence of a syrup on a water-bath and extracted with alcohol. The filtrate is then freed from alcohol by evaporation and precipitated with lead acetate and ammonia. The precipitate is collected on a filter, washed with distilled water, treated with boiling alcohol, and filtered hot, and the filtrate is treated with a few drops of sodium-hydroxide solution, then evaporated to dryness. The dried residue is then extracted with absolute alcohol, and a large excess of ether is added to the filtrate. The alkaline salts of the bile acids are thus precipitated; they are removed by filtration and dissolved in a little water, and their identity is determined by the Pettenkofer test.

Oliver's Test.—This test is one of the most delicate and probably the most reliable of all. It is an imitation of the reaction which results in a precipitation of peptone and of propeptone in the intestine, when these bodies come into contact with the bile acids. The formula of the test solution which is used is this: Pulverized peptone (Savory and Moore's), 30 grains; salicylic acid, 4 grains; acetic acid, 30 minims; distilled water, sufficient to make 8 fluidounces.

Before making this test, the urine must be perfectly clarified by repeated filtrations, acidulated, if not already acid in reaction, and reduced to 1.008 specific gravity. Twenty minims of the urine are

then run into sixty minims of the test solution. If the bile acids are normal in quantity, or if less than normal, no immediate reaction takes place, but in a short time a slight milky turbidity will appear. If the bile acids be present in excess, a distinct milkiness promptly appears, becoming more intense after the lapse of two or three minutes, the depth of opacity corresponding to the quantity of bile acid present. Agitation of the mixture causes a diminution of the opalescence or its entire disappearance, but the addition of more of the reagent causes it to reappear.

QUANTITATIVE DETERMINATION.—Oliver's test may be used for approximative determination of the quantity of biliary acid present in the following manner: A standard mixture is made by combining equal parts of the test peptone solution and normal urine reduced in specific gravity to 1.008. If then it is found that sixty minims or more of the urine to be tested must be added to the test solution in order to produce an opacity equal to that of the standard mixture, the urine does not contain an abnormal quantity of bile acid. If less is required, the following table is used to compute the quantity present as indicated by the number of minims required to produce the standard degree of opacity:

OLIVER'S TABLE.

Minims of urine required.	Drops.	Percentage of increase indicated.	ims of urine required.	Drops.	Percentage of increase indicated.
1.....	2	6,000	20.....	40	300
2.....	4	3,000	25.....	50	240
3.....	6	2,000	30.....	60	100
4.....	8	1,500	35.....	70	83
5.....	10	1,200	40.....	80	66
10.....	20	600	45.....	90	50
15.....	30	400			

Increase of bile acids above seven hundred per cent. is rare. No other substance has yet been discovered which interferes with this test, and a delicacy is claimed for it sufficient to detect one part of bile salt in eighteen thousand to twenty thousand of a sodium chloride solution.

BILE PIGMENTS.

The bile coloring matters give the urine a color which varies from yellow to greenish-yellow, even a nearly pure green, to yellowish or greenish brown or a dark brown. Shaking the urine produces a foam, the bubbles of which have a yellow or greenish-yellow tinge. A yellow color is often given also to any morphological elements that may be present in the sediment, rendering their detection with the

microscope less difficult. Bile pigments are present in the urine in nearly all conditions which produce jaundice, even a few days before the discoloration of the integument has become perceptible; but many conditions of the liver which fail to produce icterus, as well as those which produce it, cause choluria. Certain conditions of the blood and hemorrhages into the tissues may produce bile-stained urine. Poisoning by phosphorus or aniline produces a discharge of a large amount of bile coloring matter in the urine.

Tests.

1. *Gmelin's Test.*—Place in a test tube a little strong nitric acid containing some commercial yellow nitrous acid, and flow over it the urine to be examined. A layer of green will form at the line of contact, surmounted from below upwards by layers of blue, violet, red, and yellow, the green being most conspicuous, the blue least so, sometimes failing to develop.

2. *Rosenbach* modifies this test by first filtering the urine through a fine, thick filter, and applying a drop of nitric acid containing a little nitrous acid to the inside of the filter. A pale yellow spot is formed, surrounded by colored rings—yellowish-red, violet, blue, and green. The test is trustworthy and delicate.

3. *Dragendorff* places a little of the urine on a plaster-of-Paris disc, and when it has been nearly absorbed lets a drop of nitric acid fall on the spot. A ring forms about the drop of nitric acid, in which green predominates.

4. *Huppert's test* is especially useful when the quantity of bile coloring matter is small. The urine is first treated with some lime water or with calcium-chloride solution, and then with a solution of sodium or ammonium carbonate. The resulting precipitate of bile pigments may be separated with chloroform, after washing with water and acidification with acetic acid. The chloroform is colored yellow by taking up bilirubin, while the acetic acid is stained green by biliverdin.

5. *Heller's Test.*—About a drachm of pure hydrochloric acid is placed in a test tube, just enough urine is added to distinctly color it, and the two fluids are mixed. The mixture is then flowed upon a column of nitric acid, and a beautiful play of colors is produced. If the nitric acid be now stirred with a glass rod, the colors are distributed in layers throughout the entire mixture.

6. *Ultzmann's Test.*—Ten cubic centimetres of urine are treated with 3 or 4 c.c. of a strong potassium-hydroxide solution, and acidified with hydrochloric acid. If bile pigment be present, a beautiful green color is produced.

Indoxyl-Sulphuric Acid.

Indoxyl-sulphuric acid, or *urine indican* ($C_8H_7NSO_4$), termed by Heller uroxanthin, has already been referred to as occurring in normal urine in combination with potassium. Owing its origin to indol, which in turn comes from the putrefaction of proteids, it is more abundant when the individual subsists largely on animal food, but its quantity never varies to any great extent in health.

Indican is increased in the urine of children suffering from severe diarrhœal disorders; and it occasionally becomes very abundant in such conditions as Addison's disease, cholera, typhoid fever, dysentery, chronic tuberculosis, acute general peritonitis, suppurative bronchitis (bronchiectasis), empyema, diabetes, disease of the spleen, carcinoma of the liver, multiple lymphomata, in certain affections of the nervous system, and in intestinal obstruction. A peculiar feature of its occurrence in intestinal obstruction is the fact that it usually becomes extremely abundant when this occurs in the small intestine, while in obstruction of the large bowel its quantity is increased only when the upper portion of the ileum is much obstructed.

Tests.

Heller's Test.—To a drachm of hydrochloric acid in a small wine-glass or beaker add slowly, with constant stirring, about twenty drops of the urine. If the indican be normal in quantity, a pale yellow or yellowish-red color is produced; but if it be markedly increased, a blue or violet color appears, the color change occurring more rapidly as the quantity of indican is greater, one or two drops of the urine sometimes being sufficient to produce the reaction. The addition of two or three drops of nitric acid renders the test more delicate.

MacMunn's Test.—Equal parts of urine and hydrochloric acid, with a few drops of nitric acid, are boiled together, cooled, and agitated with chloroform. If much indican be present, the chloroform takes a violet color. On spectroscopic examination, this liquid shows an absorption band before *D*, due to indigo blue; and one after *D*, due to indigo red.

Jaffe's Test.—Ten cubic centimetres each of urine and hydrochloric acid are mixed in a test tube, and while being shaken a fresh solution of the chloride of lime or chlorine water is added, drop by drop, until the deepest obtainable blue color is reached. The mixture is then shaken with chloroform, which readily dissolves the

indican and holds it in solution, the depth of color being an index to the quantity of indican present.

Albumin, if present, must be removed before applying these tests, because it sometimes forms a blue color on standing with hydrochloric acid. The appearance of a red color instead of blue denotes the presence of iodine.

Hydroxybutyric Acid.

Hydroxybutyric acid ($C_4H_8O_3$) is a monobasic acid of the lactic-acid series, existing in its pure state as a crystalline solid, but in the form of a syrup when obtained from the urine. This syrup is odorless and is readily miscible with water, alcohol, and ether. It is not precipitated by lead acetate or ammoniacal basic lead acetate, and possesses dextrorotatory power over polarized light, sometimes interfering with the polarimetric estimation of glucose. When boiled with water in the presence of a mineral acid, it is decomposed into α-crotonic acid and water.

Hydroxybutyric acid is usually accompanied in the urine by diacetic acid, and sometimes by acetone, being especially likely to occur in advanced cases of diabetes mellitus. It has been found also in the urine during measles, scarlatina, scurvy, and in diseases of the brain.

Test.

If the urine remains dextrorotatory after complete fermentation with yeast, hydroxybutyric acid is probably present.

Külz does not regard the substance separated from the urine identical with either of the four forms of this acid, but describes it under the name of pseudo-oxybutyric acid. His method of detecting it is as follows: Evaporate the urine after complete fermentation to a syrupy consistence, add an equal volume of concentrated sulphuric acid, and distil immediately, without cooling. The distillate containing α-crotonic acid is collected by strong cooling, and crystals separate, which melt at 72° C., a characteristic of hydroxybutyric acid. If no crystal can be obtained, shake the distillate with ether, evaporate the ether, wash the residue with the water that remains, and test the melting point.

The Diazo Reaction.

The diazo reaction, introduced by Ehrlich as a valuable aid in the diagnosis of certain diseases, particularly of typhoid fever, depends upon the fact that there is present in the urine during these diseases a certain aromatic substance, of a nature not yet known, which is

capable of uniting with freshly prepared diazosulphobenzol to form aniline colors.

According to the original claims of Ehrlich, which have been abundantly confirmed, the reaction is most commonly found in the urine of typhoid fever from the fourth to the seventh day and thereafter. If the reaction do not occur, the diagnosis is doubtful; if it be faint and occurring for only a few days, the prognosis is favorable. It is found only in such cases of pulmonary tuberculosis as are pursuing a rapidly fatal course. It sometimes but not often occurs in measles, miliary tuberculosis, pyæmia, scarlet fever, and erysipelas; but never in afebrile diseases, such as chlorosis, hydræmia, diabetes, or in diseases of the brain, spinal cord, liver, or kidneys.

The Diazo Test.—Diazosulphobenzol is formed by the action of nitrous acid on sulphanilic acid. In order to obtain it in a fresh state, the sulphanilic acid is kept in a solution with hydrochloric acid; to this a solution of sodium nitrite is added, in order to liberate nitrous acid and form the diazosulphobenzol. The following solutions are therefore required:

1. Sulphanilic acid, 2 gm., and hydrochloric acid, 50 c.c., in 1,000 c.c. of distilled water.

2. A 0.5-per-cent. solution of sodium nitrite.

Mix one part of No. 2 with fifty parts of No. 1, add to the mixture an equal volume of the urine, render strongly alkaline with ammonia, and shake well. The characteristic reaction consists in the formation of a carmine-red color both in the mixture *and in the foam*. A greenish precipitate is thrown down after the mixture has stood twenty-four hours. Normal urine yields a yellow color.

Gases.

Pneumaturia is the name given to the escape of atmospheric air or gases through the urethra. This phenomenon may result from the entrance of air or intestinal or other gases into the bladder by whatever means.

In another class of cases the gas is formed in the urine and is, in part or wholly, held in solution. Carbon dioxide, hydrogen, and methane, for example, result from the action of bacteria on the carbohydrates, particularly on the glucose, in diabetic urine. The yeast fungus, the bacillus coli communis, the bacillus of butyric-acid fermentation, and a number of others have been discovered in the urine of these cases. Ralfe reports a case in which spontaneous ebullition of a large quantity of an odorless gas, believed to be carbon dioxide, occurred, probably as a result of a decomposition of glucose or ace-

tone, as the urine contained sugar. (For method of detecting carbonic acid in the urine see p. 704.)

Hydrogen Sulphide.

Hydrogen sulphide (H_2S) is the most important of the gases thus voided, since its appearance always denotes a possibility of the existence of a serious lesion.

Hydrothionuria has been attributed to either of three principal causes: (*a*) To the action of bacteria upon albuminous bodies in the urine; (*b*) to an exosmosis of the gas from the intestine or from a pus sac into the bladder; or (*c*) to its absorption by the blood and subsequent elimination through the kidneys. An additional cause is illustrated in a case reported by Rosenheim and Gutzmann, in which the autopsy developed a direct communication between an abscess cavity and the bladder by a fistulous opening. These authors also believe it possible that sulphuretted hydrogen may be liberated in the bladder by decomposition of hyposulphurous acid, which belongs to a class of sulphur compounds normally present in the urine, and is easily decomposed.

Friedrich Müller objects to the theory of its diffusion through the bladder wall, attributing it chiefly to the action of bacteria on the proteids; he also describes two bacteria, a round and an oval coccus, which he has found capable of producing hydrogen sulphide in the urine. The latter theory is supported also by the observation of Ranke, that if a few drops of urine containing sulphuretted hydrogen be added to normal urine, the formation of this gas is established in it, and that a few drops of this urine would communicate the "fermentation" to a third specimen.

The urine is usually acid in reaction, of yellow color, comparatively low in specific gravity, albuminous, turbid from the presence of bacteria, and communicates the characteristic, offensive odor of hydrogen sulphide; it is sometimes, however, red, of high specific gravity, and free from albumin or bacteria.

Clinical Significance.—A study of the comparatively few cases of hydrothionuria which have been reported indicates that the following causes predominate in its production: Abscesses containing decomposing pus, located in the immediate vicinity of the bladder or communicating with it; abscesses in the ischiorectal fossa, in the sigmoid flexure, the vermiform appendix, the intestine, rectovaginal fistula, with escape of fæces into the vagina (probably leading to infection through the urethra); an enlarged prostate, causing a diverticulum of the bladder to press upon the rectum; perforation of gas-

tric or intestinal ulcers, gonorrhœal pyosalpinx, and vesical catarrh in the presence of bacterial infection. It has been encountered also in a case of smallpox, in gastric and gastrointestinal catarrh resulting from errors of diet or excessive drinking, in a case of pulmonary gangrene with feculent cystitis, and in diabetes mellitus (Von Noorden). In the last instance the presence of sulphuretted hydrogen in the urine must be attributed to a decomposition of some sulphuretted body, particularly albumin, associated with glucose in the urine.

J. Foster Scott, who has made an exhaustive investigation of this subject and its literature, reports in the *New York Medical Journal* (Vol. LVII., p. 663, 1893) two instances in which hydrothionuria followed puerperal eclampsia in the same subject, each time with the delivery of a dead fœtus, the urine containing at the same time albumin and vibriones; a third case in which it followed a laparotomy for pyosalpinx, the urine being non-albuminous and free from organized deposit or bacteria; and a fourth case in which it followed a normal labor, without particular disturbance of health, and in urine free from albumin, blood, or bacteria.

Tests.

The presence of hydrogen sulphide in the urine could hardly escape recognition, owing to the characteristic and obtrusive nature of its odor. It may be demonstrated, however, by either of the following tests:

1. To about two inches of urine in a test tube add a few drops of silver-nitrate solution; a white precipitate of chlorides and albumin immediately falls. Then add a few drops of nitric acid; a dark-gray color develops, becoming almost black; and, finally, a dark ring of silver suphide is deposited on the glass.

2. Add a single drop of lead acetate to about two inches of urine in a test tube. An inky-black precipitate of lead sulphide (PbS) is formed, with a dark-brown supernatant fluid (Scott).

3. Heller's test: Add to the urine a few drops of ferric-chloride solution. A black precipitate is formed, or only a brown discoloration if the quantity of hydrogen sulphide be very small.

4. A silver or lead rod immersed in the urine for a few hours will become blackened. (A case has been reported in which a silver catheter used to withdraw the urine was discolored.)

Drugs in the Urine.

Arsenic.

1. *Reinsch's Test.*—Add to the urine in a test tube a few drops of pure hydrochloric acid; then introduce a small piece of pure,

bright copper foil, one-eighth or one-sixteenth inch square, and boil for several minutes. If arsenic be present, a dark iron-gray coating is deposited on the copper. The test is more likely to be successful if the urine be first concentrated by evaporation at a moderate temperature.

2. In order to detect small quantities of arsenic, the distillation method may be used. For this method, about 500 c.c. of urine are strongly acidulated with pure hydrochloric acid, and the mixture is allowed to digest for several hours. It is then placed in a retort, fitted with a long condensation tube, which is kept cold with ice or with sheets of filter paper, constantly moistened with cold water, and terminating in a loosely stoppered flask containing a little distilled water. Heat is applied to the retort and the distillation is carried to almost complete condensation of the urine.

The distillate is then submitted to the tests for arsenic; first by the preceding Reinsch method, then by Marsh's test. If the quantity of arsenic has been sufficient by the first test to cause precipitation on the copper foil, however, the Marsh test may be employed without distillation.

Lead.

As a preliminary test, strips of filter paper wet with the urine may be submitted to a stream of hydrogen sulphide. If lead be present in considerable quantity, the paper is stained by the formation of lead sulphide; or a stream of hydrogen sulphide may be passed through the urine. If a black precipitate is produced, this may be collected on a filter, washed, and boiled for fifteen minutes in a twenty-per-cent. aqueous solution of nitric acid. The liquid is then filtered and evaporated to dryness, the residue is dissolved in water, and the tests for lead are applied to the solution. To a part of the solution add sulphuric acid. A white precipitate is formed, which is soluble in potassium hydroxide solution (which must be free from lead). The addition of ammonium sulphide to this alkaline solution causes it to turn black.

This test may also be applied by evaporating the urine to dryness, destroying the organic matter by heat, and dissolving the residue by boiling with nitric acid, filtering, and proceeding as just described.

Wood's Method.—This is probably the most delicate test yet devised. For four or five days before securing the specimen of urine for examination, the patient takes from five to ten grains of potassium iodide three times a day. A litre of urine is then obtained, evaporated to dryness, and fused in a crucible with a little pure potassium nitrate until it becomes white. When cool, the residue is

extracted with hot dilute hydrochloric acid, filtered, the filtrate rendered alkaline with ammonia to precipitate the phosphates and iron. Ammonium sulphide is now added to precipitate the lead, the precipitate is washed three times with hot distilled water and decanted, water acidified with hydrochloric acid is added, and the whole is allowed to stand until the next day. It is then filtered through a small filter, the precipitate is washed, and a little nitric acid is added, drop by drop, to dissolve the lead and carry it through as a nitrate. The filtrate is collected in a watch-glass and evaporated to dryness, and the final test is made by adding a drop of water and a crystal of potassium iodide. The formation of a yellow precipitate denotes the presence of lead.

Mercury.

1. *Jolles' Method.*—Granulated gold is first prepared by the following method: From 16 to 20 gm. of pure gold chloride are dissolved, the solution is heated, and burned magnesia is added with constant agitation, until the fluid above the precipitate becomes colorless. Heat is applied for a few minutes, the fluid is decanted, and the precipitate is washed until the wash-water shows no trace of chlorine. The gold-magnesium compound is then dried and treated with strong nitric acid. This is warmed over a water-bath until the fluid becomes clear and colorless. The precipitate is thoroughly washed, dried, incinerated in a crucible, and finally glowed with a blow-flame. About 2 gm. of this granulated gold are then placed in from 100 to 300 c.c. of the urine, 3 c.c. of pure hydrochloric acid being added; the mixture is heated, and from 2 to 3 gm. of freshly prepared stannous chloride are added. If a flaky precipitate of the hydrated oxide of tin is formed, there is too little hydrochloric acid, and the error must be corrected. The mixture is then warmed to 70° or 80° C., and from 30 to 50 c.c. of a saturated stannous-chloride solution are added. A cloudiness denotes the presence of mercury.

2. To a litre of urine add 10 c.c. of hydrochloric acid, introduce a little piece of copper foil, and apply heat. After letting the fluid stand for twenty-four hours, remove the copper foil, wash it with water, alcohol, and ether, and let it dry. Then introduce it into a long test tube and heat it to redness. If mercury be present, it condenses on the cool parts of the tube. If fumes of iodine be now introduced, the mercury is changed into mercuric iodide, having a red color.

Bromine and Iodine.

Add to the urine a little fuming nitric acid or some freshly prepared chlorine water, and shake with chloroform. If bromine be

present, the chloroform assumes a brownish-yellow color. If iodine be present, a carmine-red or purple color is produced. Gillet states that this test fails in ammoniacal urine, owing to the reaction of the iodine on the salts of ammonia, with formation of nitric iodide and iodic acid, the nitric iodide again splitting up into iodic acid and nitrogen. He suggests the addition of potassium-hydroxide solution to the urine before making the test in order to prevent this combination.

Quinine.

1. If to a solution containing quinine chlorine water be added, then potassium ferrocyanide, and finally ammonia, a red color is produced.

2. Add to about 10 c.c. of urine in a test tube a drop or two of hydrochloric acid, then two drops of chlorine water or of bromine water, and an excess of ammonia. An emerald-green color is produced, which corresponds to the quantity of quinine present. Carefully neutralize the mixture, and the color changes to blue; add an excess of an acid and it changes to a purple or red color; again add an excess of ammonia, and the green color returns.

Acetanilide (Antifebrin).

Evaporate the urine to about half its volume, add hydrochloric acid, and boil for a few minutes; extract with ether, evaporate the ether, treat the residue with distilled water, adding a few cubic centimetres of an aqueous solution of phenol and half as much of a one-per-cent. solution of hypochlorite of lime. A pale-green (onion peel) color is produced, which changes to blue on the addition of ammonia (iodophenol reaction). If the urine is of pale color, the extraction with ether may be omitted.

Naphthalin.

1. The addition of sulphuric acid to acid urine containing naphthalin produces a green color.

2. Add to the urine a few drops of ammonia or of sodium-hydroxide solution. A blue fluorescence is produced, owing to the production of β-naphthol, changing to a yellow color on the addition of calcium-chloride solution and hydrochloric acid.

3. Urine containing naphthalin becomes darker on standing a few days, and will then yield a red hue on the addition of acetic acid.

Antipyrin.

1. If antipyrin be also present in the second test for quinine, the urine acquires a red color on the first addition of ammonia. The coloring matter can be removed from the solution by shaking it immediately with chloroform or alcohol. If the chloroform solution be shaken with acidulated water, an orange-pink color is produced. If the solution be now rendered alkaline, the color changes to violet-pink. Carrez states that this reaction may be employed for the detection of antipyrin in the urine.

2. The addition of ferric chloride to urine containing antipyrin produces a red color.

Morphine.

1. Nitric acid added to a moderately strong solution of morphine produces a slowly developing orange-red color. This test is not positive, however, owing to the red color often produced by the addition of nitric acid to normal urine, and the comparatively small quantity of morphine usually found in the urine. The reddish color due to morphine, however, shows more yellow and develops more slowly than that which occurs in normal urine.

2. Add to the urine a little chloroform containing one or two drops of iodic acid. As the chloroform sinks to the bottom iodine is taken up by it and acquires a pink color, corresponding in depth to the quantity of morphine present. Now add enough ammonia to render the mixture alkaline; the pink color is discharged from the chloroform and the supernatant fluid becomes deep brown.

If the urine be first rendered alkaline with sodium bicarbonate and iodic acid added, shaking the mixture with chloroform produces a violet color.

Salicylic Acid.

The addition of 1 c.c. of strong ferric-chloride solution to 10 c.c. of urine containing salicylic acid (salicyluric acid) produces a violet color. The same color change is sometimes produced, however, by the addition of ferric chloride to diabetic urine.

Santonin.

The urine has a bright-yellow color which turns red on the addition of an alkali, the color gradually fading. On the addition of baryta water and filtering, the color passes through with the filtrate. It is not taken up by ether.

Rhubarb and Senna.

These preparations give the urine a yellow color, probably due to the presence of chrysophanic acid, which is changed to red on the addition of an alkali; but the color is permanent. On the addition of baryta water and filtering, the color remains with the precipitate and will be taken up by ether.

Pine Acids.

The acids or salts of pine appear in the urine after the ingestion of balsams, cubebs, and sometimes after turpentine has been taken. The addition of strong nitric or hydrochloric acid causes a precipitation resembling that of albumin, but if it be treated with strong alcohol it is dissolved. Urine containing turpentine has frequently an odor of violets.

Urinary Sediments.

Freshly voided normal urine is free from sediment; as it cools, however, a flocculent deposit collects about the bottom of the vessel, consisting of mucus, usually holding in suspension a few epithelial cells. Subsequent changes in the urine lead to the deposit of a more or less abundant sediment. In acid urine we find at first a deposit of reddish-yellow or clay-yellow amorphous urates of potassium, sodium, and ammonium, with sometimes those of calcium and magnesium, a sediment which is readily dissolved by heat. A little later a part of this sediment is transformed into brick-red or dark-brown, well-defined crystals of uric acid; and along with these, or perhaps a little later, we find small octahedral crystals of calcium oxalate. At a still later period, varying usually from two to four days after the urine is voided, and depending greatly upon the temperature at which the urine is kept, we have the results of the alkaline fermentation in a deposit of the alkaline earths, amorphous calcium phosphate, and prismatic (coffin-lid) crystals of the triple phosphate of ammonium and magnesium, sometimes accompanied by the dark, spiculated spherules of ammonium urate (mulberry crystals).

In normal alkaline urine the earthy phosphates often form a rather abundant precipitate as the urine becomes cold. This sediment is quickly dissolved by the addition of a few drops of a strong acid.

Pathological urine frequently contains one or more of the elements just mentioned in suspension when voided, almost immediately forming a sediment. But in addition to these we may find quite a large

number of either chemical or biological substances in the urine, as crystals of leucin, tyrosin, xanthin, blood, pus, bacteria, etc.

The best classification of urinary sediments divides them into two classes, chemical and anatomical sediments. The first class includes uric acid, urates, calcium oxalate, cystin, leucin, tyrosin, xanthin, and phosphates. The principal anatomical elements, which are almost always pathological in character, are pus corpuscles, blood, renal casts, spermatozoa, fragments of neoplasms, and bacteria.

The microscope furnishes us the principal means of examining the sediments; chemical manipulations are sometimes resorted to, but chiefly for the purpose of confirming the results of microscopic investigation.

Sedimentation.—Until recently we had no means of hastening the sedimentation of urine. It had to be left to the slow process of gravitation, which required from a few hours to a day or more, and frequently resulted in the loss of important morphological characteristics. Spontaneous sedimentation is best accomplished by placing the urine in a conical glass, having nearly perpendicular sides, and setting it in a cool place, securely covered to protect it from dust. If the urine be but faintly acid, and particularly if the purpose of the examination is the study of its organized constituents, a little hydrochloric acid should be added to counteract the alkaline fermentation, since many elements are dissolved by alkalies. To prevent the growth of bacteria, a little chloral, salicylic acid, resorcin, or formalin may be added, unless chemical tests are to be made of the same specimen.

Sedimentation by means of the centrifugal apparatus is by far the most satisfactory method, since it is both quicker and more positive in its results. By it we obtain without difficulty a separation of all the morphological elements of the urine at a time when decomposition has not affected them. Several kinds of centrifuge are offered by the instrument dealers. The most satisfactory of all is the electrical centrifuge of Dr. Purdy, which enables one to use a larger quantity of urine and to produce a greater speed of revolution than is possible with those which are operated by hand power. The tubes of most instruments are graduated to hold only 10 c.c., sufficient for the examination of sediments, but hardly sufficient for use in the sedimentation and estimation of chemical precipitates.

The sediment should be removed from the glass or centrifuge tube by a pipette with a long and very narrow point, care being taken to withdraw as much of the sediment as possible with little fluid. A very small drop of the sediment is then placed on the microscope-slide for examination.

Organized elements of the sediment may be obtained in a pure

state by acidulating the urine with acetic acid before sedimentation, and afterwards washing the sediment in a physiological salt solution, which may be used warm if necessary, to remove urates. The sediment may be preserved for future use by pouring over it a mixture of equal parts of glycerin and water, to which two per cent. of a saturated solution of thymol has been added.

Chemical Sediments.

Uric Acid.

Uric-acid crystals are found almost exclusively in acid urine, and may frequently be recognized by the naked eye clinging to the sides of the vessel after standing or to foreign particles in the urine. It is

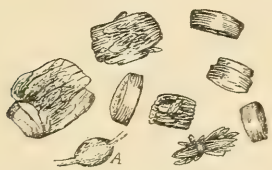

Fig. 52.—Uric-Acid Crystals. *A*, Crystallization on a Cotton Fibre.

Fig. 53.—Uric-Acid Crystals More Highly Magnified. *A*, Crystallization on a Cotton Fibre.

this tendency to crystallize upon foreign matter that leads to the frequent production of uric-acid calculi. Uric-acid crystals are for the most part rhomboidal in shape, but may be rectangular, or, having rounded extremities, they may appear ovoidal or circular. They are usually flattened, but sometimes appear to be almost perfect cubes. The union of several crystals often produces stars and variously formed clusters (Figs. 52 and 53). They are the only crystals in urine which have a yellow color; they may vary from a dark orange or brownish-yellow to a pale yellow, but they are never colorless. Uric-acid crystals cannot be considered abnormal in quantity, because of spontaneous crystallization, unless this occurs within six hours after the urine has been voided and in unusually large quantity.

Urates.

The acid urates of sodium and potassium may be found in the sediment of acid urine, rarely also that of calcium. Ammonium urate is nearly always found in alkaline urine.

Sodium urate is oftenest found in the form of amorphous granules, which compose the "brick-dust" deposit and are very insoluble; but it sometimes occurs in the form of fan-shaped or stellate clusters of needle-like crystals. Potassium acid urate occurs only in amorphous form, constitutes a part of the amorphous urate deposit, and is more soluble than the sodium salt. Calcium acid urate occurs rarely, in acid urine only, and in small quantity, as an amorphous, white or grayish, very insoluble powder. Heated to fusion, it is converted into calcium carbonate.

Ammonium urate occurs in dark-brown crystalline spheres,

Fig. 54.—Crystals of Ammonium Urate.

studded with fine spiculæ of various lengths, which are known as "mulberry" or "thorn-apple" crystals (Fig. 54). It occurs, as a rule, in alkaline urine and in company with amorphous calcium phosphate and triple-phosphate crystals. It is the only urate deposit found in alkaline urine.

Mixed Urates.

This "brick-dust" or "Cayenne-pepper" deposit consists of a granular sediment, having a reddish color, darker than that of the urine in which it is found. It usually forms rapidly as the urine cools, and may remain suspended, forming a pellicle on the surface and clinging to the sides of the vessel to form a ring. It is readily dissolved by heat, caustic alkalies, and mineral acids.

Significance.—The deposit of mixed urates by no means always signifies a pathological condition, for it is often found in normal urine that has stood over night in a cold room, especially in winter. Pathologically, however, it occurs in febrile states, in emaciating diseases of the viscera, especially of the liver, in functional disorders of the stomach, and during the acute stage of gout.

Calcium Oxalate.

Oxalate of lime is encountered in the sediment of either acid or alkaline urine, often associated on the one hand with uric acid or

urates, or with the triple-phosphate crystals on the other, and sometimes with albumin, the presence of which has been attributed to the injury produced by the sharp oxalate crystals in their passage through the urinary tract. Two forms of calcium-oxalate crystals are found: First, beautiful, small, highly refracting, octahedral, "envelope-shaped" crystals; second, a probably transitional form of circular or ovoid discs, with central depressions or "dumbbell crystals" (Fig. 55).

Fig. 55.—Calcium-Oxalate Crystals.

Although these crystals may usually be distinguished from all others without difficulty with the microscope, confusion may arise in the presence of imperfectly formed triple-phosphate crystals. A drop of acetic acid allowed to flow under the cover-glass readily differentiates between them by dissolving the triple phosphate. Calcium-oxalate crystals resist the action of acetic acid, alcohol, water, ether, and alkalies, but they are dissolved by mineral acids. They are differentiated from dumbbell uric-acid crystals by the absence of color and by their insolubility in alkalies.

Phosphates.

Only the alkaline phosphates are found in urinary sediments. These occur as triple phosphates of ammonium and magnesium or as calcium phosphate. Two forms of triple-phosphate crystals may be encountered, but the form most frequently seen is a triangular prism

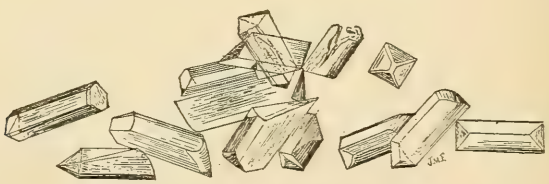

Fig. 56.—Crystals of Ammonium-Magnesium Phosphates (from a camera-lucida sketch). The crystal at the extreme left is probably calcium phosphate.

having bevelled ends, the "coffin-lid" crystals (Fig. 56). These crystals are sometimes defective, lacking part of their length and appearing almost square, or one or more corners may be absent. The other form is rarely met with and consists of rosettes or star-shaped bunches of feathery crystals often resembling fern leaves, and probably representing an early stage of crystallization. They are found in alkaline urine. When an acid reaction is detected in urine containing triple phosphates it is probably due to the fact pointed out

by Bruns, of New Orleans, that the upper stratum of the urine is acid, while the lower containing the phosphates has become alkaline.

Calcium phosphate occurs either as a whitish, flocculent sediment which the microscope resolves into irregular collections of minute, nearly colorless granules; or, less frequently, in crystalline form. The crystals are rod-shaped when single, or are arranged in clusters of various forms, rosettes, stars, sometimes closely massed into clubs or wedges in which the lines of crystallization may remain visible.

Phosphatic sediment is most frequently found when the urine is alkaline owing to the presence of a fixed alkali or to excess of the earthy phosphates themselves, but the triple phosphates originate in a union of volatile alkali, ammonia, and magnesium phosphate.

Significance.—When a phosphatic precipitate occurs in urine which is alkaline from a fixed alkali, we usually find chiefly calcium phosphate, alone or with some triple-phosphate crystals. The urine when voided is generally cloudy, of high specific gravity, and alkaline, liberating gas on the addition of an acid. This condition is found in the debility of convalescence, especially after acute disease, or in affections attended by feeble respiration. It may arise from disordered digestion with fermentative decomposition of food, manifested by flatulence, constipation, frequent micturition, sallowness, and despondency, headache, backache, and emaciation. In the so-called phosphatic diabetes, the deposit of calcium phosphate results from excessive elimination, the urine being abundant, alkaline, and containing a dense white deposit. Roberts regards the deposit of calcium phosphate in some instances as an indication of a grave disorder, cancer of the pylorus, tuberculosis, or it may result from such a condition as exhaustion from acute rheumatism.

The phosphatic deposit which results from a volatile alkali, the triple phosphates, is a result of the decomposition of the urine somewhere in the urinary passages, and is often accompanied by pus and mucus. The symptoms which belong to the condition are those which result from suppurative diseases in general, or from inflammatory and obstructive conditions of the urinary passages in particular, such local conditions as calculus or stricture, enlarged prostate, surgical kidney, or it may be a disease or injury of the spinal cord.

Cystin.

Cystin ($C_3H_6NSO_2$), closely related to taurin and probably derived from the liver, is one of the least frequent ingredients of urinary deposits. It occurs either in six-sided tabloid crystals of opalescent

lustre, with tracings of secondary crystallization, and often arranged in clusters or in highly refracting, nearly rectangular plates. The crystals are soluble in caustic alkalies, in oxalic acid, and strong mineral acids. They may be differentiated from uric-acid crystals, which they sometimes resemble, by the fact that a drop of ammonia run under the cover-glass causes their solution, from which they recrystallize when the ammonia has been removed by evaporation. This test yields ammonium urate with uric-acid crystals. Oxalic acid or hydrochloric acid applied in this manner dissolves cystin, but not uric acid.

Significance.—Little can be said in regard to the significance of cystinuria further than that it has been observed in chlorotic women, strumous children, and in association with hepatic disorders and grave renal disease. It has been observed to prevail in certain families. Cystin is not infrequently an ingredient of vesical calculi.

Leucin and Tyrosin.

Leucin ($C_6H_{13}NO_2$) and tyrosin ($C_9H_{11}NO_3$) are closely related products of the decomposition of proteids or of their derivatives.

Leucin occurs in yellowish, highly refracting spherules, resembling fat globules, though less refracting; but in a pure state it crystallizes in irregular scales or rosettes, having a greasy feel. Cystin spherules may be distinguished from oil globules by their insolubility in ether. They are partly soluble in water and alcohol, however, completely soluble in caustic alkalies, and insoluble in mineral acids.

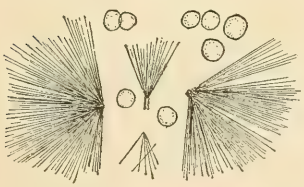

Fig. 57.—Leucin Spherules and Tyrosin Crystals.

Tyrosin crystallizes in the form of fine needles arranged in sheafy bundles; sometimes in alkaline solution in the form of rosettes (Fig. 57). It is readily soluble in hot water, acids, and alkalies; feebly soluble in cold water, and insoluble in alcohol and ether.

Leucin and tyrosin are found in the urine in some cases of prolonged suppuration or gangrene, in acute yellow atrophy of the liver, phosphorus poisoning, leucocythæmia, typhoid fever, tuberculosis, and rarely in cases of smallpox. Ulrich has found them repeatedly in normal urine. Bouchard attaches the greatest importance to leucin in all cases of "uræmia," believing that the toxic symptoms are attributable to leucin poisoning rather than to urea poisoning.

Melanin.

This substance is a black pigment, containing carbon, nitrogen, iron, and sulphur. It occurs as a sediment in small granules, which are insoluble in cold alcohol, ether, acetic acid, and dilute mineral acids; but soluble in boiling acetic, lactic, and mineral acids, and in strong solutions of ammonium, sodium, or potassium hydroxide. The urine containing melanin is not always dark colored when voided, but becomes so on exposure to the air or when treated with such oxidizing agents as sulphuric or hydrochloric acid or ferric chloride. The addition of bromine water to the urine containing it produces a yellow precipitate, which gradually becomes black. The addition of a solution of ferric chloride yields a dark-brown cloudiness or a precipitate which is redissolved by an excess of the reagent, the extent of the reaction corresponding to the quantity of melanin present. The addition of a solution of sodium nitroprusside, followed by potassium hydroxide, produces a pink or red color, which turns blue on the addition of an acid, the reaction being due, however, to the presence of some other substance which accompanies the pigment, and not to the melanin itself.

Melanuria is an almost constant feature in the presence of melanotic sarcoma or carcinoma, but sometimes occurs in intermittent fever of chronic type and in wasting diseases.

Fat.

A small amount of fatty matter, palmitin and stearin, is present in normal urine; it is somewhat increased in the urine of pregnant women, and probably sometimes as a result of the ingestion of much fat with the food. It appears in the urine in the form of highly refracting globules of various sizes, with dark margins, which are soluble in ether, benzol, chloroform, carbon disulphide, and hot alcohol. Much fat, as occurs in chyluria, gives the urine a milky appearance, which is cleared up by shaking it with ether. Chylous urine often has a pinkish color, owing to admixture of blood, and on standing yields a thick, supernatant layer resembling cream, with a reddish sediment. Oil globules are not seldom discovered in the urine of chronic parenchymatous nephritis; oftener in that from the large, white, fatty kidney in phosphorus poisoning and in diabetes mellitus. Ebstein found fat in the urine in a case of hydronephrosis; Henderson in three cases of heart disease. Free fat may occur from the passage of fatty casts or fatty epithelium. Lipuria sometimes oc-

curs in pancreatic disease, and may precede the appearance of fatty stools. It has been observed in acute yellow atrophy of the liver, accompanied by renal degeneration. It is often produced by bone fractures, especially in comminuted fractures and during their repair.

Anatomical Sediments.

Epithelium.

A greater or less number of epithelial cells are almost invariably found in urinary sediments, whether the urine be normal or pathological. Those found in normal urine come, for the most part, from the bladder and urethra. An attempt is no longer made to distinguish with precision between the different types of cells, with a view to de-

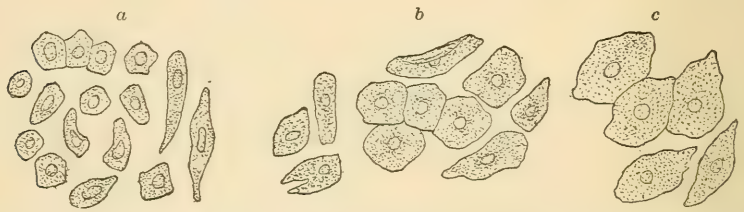

Fig. 58.—Types of Epithelium Found in Urinary Sediment. *a*, From the kidney and ureter; *b*, from the bladder; *c*, from the vagina.

termine their origin. Each division of the urinary tract has its typical surface epithelium; but of no cell can it be said that it is found in one division alone, especially in the presence of a diseased condition, for immature or transitional cells from the deeper layers may then appear in the urine.

There are three principal types of cells: 1. Small, round, spheroidal, granular cells, having comparatively large nuclei and excentrically located nucleoli, occurring singly or in attached groups, and not infrequently showing fatty degeneration as a result of disease. This type of cell is found in the convoluted tubule of the healthy kidney, but may come also from the deeper layers of the mucous membrane of the renal pelvis, bladder, ureter, or male urethra. They are larger than pus cells and have but a single nucleus. It is only in the presence of albuminuria and other evidences of renal disease that their origin can be referred to the kidney.

2. Nucleated columnar epithelium, irregularly spindle, conical, cylindrical, or caudate in form, the cells occurring singly or in groups. They may be derived from the superficial layer of the mucous membrane of the renal pelvis or from the deeper layers of the

ureters, bladder, or urethra—from any part of the urinary tract but the kidney.

3. Large, flat, irregular or rounded, squamous or pavement epithelium, having a single distinct nucleus, usually centrally located. These are derived from the bladder or from the vagina, the vaginal cells being usually larger than those of the bladder.

Significance.—Although the type of epithelium discovered in the urinary sediment does not furnish us positive evidence of the region affected, it nevertheless affords us, in many instances, valuable information of the character of the disease. In acute congestion of the kidney, for example, and in acute parenchymatous or diffuse nephritis, especially in the scarlatinal form of the disease, a large number of spherical epithelial cells from the convoluted tubules appears in the urine, most of the cells as a rule being nearly normal in appearance. The same cells appear in the chronic form of diffuse nephritis, but in a more or less degenerated condition, containing fat in granular form, sometimes in minute globules. Not infrequently the cells are more or less disintegrated, appearing in fragmentary form. They often adhere to renal casts, or apparently of themselves form the casts. Chronic interstitial nephritis is characterized by an almost entire absence of renal epithelium in the urine. The same is true of amyloid disease of the kidney, when uncomplicated. In pyelitis and disease of the pelvis of the kidney much epithelium is found, both of the round-celled variety and of the spindle or caudate cells, the latter being of especial diagnostic value. In cystitis and other inflammatory diseases of the bladder the flat cells predominate, columnar cells being also found when the disease is so severe as to cause desquamation of the deeper layers of the mucous membrane.

Pus.

Pus may enter the urine from any part of the urinary tract and appear as a sediment. It may come from the free mucous surface, from an ulcer, or from inflamed tissues. The urine is turbid when voided, and yields the reactions of albumin. No positive distinction can be made between the appearances of pus corpuscles, leucocytes, and lymph cells. The pus cells appear as pale, finely granular, spherical cells, about as large as a leucocyte, containing a single nucleus, often two or three nuclei. Water causes them to swell and become more delicate in outline; acetic acid acts in the same manner, at the same time rendering the nuclei more distinct and causing the granular matter to disappear. As urinary sediment pus cells are dead and do not exhibit the amœboid movements which they may

have in a fresh state. Ammonium and potassium cause pus corpuscles to swell and coalesce into a glairy, sticky mass, in which the nuclei only are visible with the microscope. Hence, in the presence of ammoniacal decomposition of the urine, pus cells may not be discovered on microscopic examination, but the pus will be found as a slimy mass, so tenacious as to adhere to the sides of the vessel. This fact is the basis of Donnes' test for pus, which is made by pouring off the supernatant fluid and treating the sediment with liquor potassæ. A sticky, gelatinous mass is found if the deposit be pus.

Quite a number of substances have been found as ingredients of pus, chiefly albuminous bodies, the most abundant of which is nucleoalbumin. Lecithin, cholesterin, xanthin bodies, fat, soaps, and cerebrin have been isolated, and another albuminous body which coagulates at 49° C. In pus from old stagnated abscesses there are peptone, leucin, tyrosin, fixed and volatile fatty acids (formic, butyric, and valerianic), and pyin.

Hottinger has shown that from 40,000,000 to 150,000,000 pus corpuscles may be discharged in the urine in a single day from an individual whose blood would not afford more than from 25,000,000 to 50,000,000 leucocytes, thus affording a strong argument in support of the local origin of pus.

The turbidity of urine containing pus may be mistaken for that due to earthy phosphates or granular urates. From the former it is distinguished by the addition of an acid which dissolves earthy phosphates, but coagulates the albuminous constituents of pus; from the urates it may be distinguished by heat, which also coagulates albuminous substances but dissolves urates.

Clinical Significance.—This is exceedingly variable. We must first ascertain the source of the pus, which is sometimes possible from the presence of accompanying distinctive substances. Pus from the kidney is more usually present in acid urine, is more uniformly mingled with the urine when voided than is that from the lower passages, and may be accompanied by round epithelial cells and casts, the latter being of especial diagnostic significance; the absence of vesical symptoms is also important. The most frequent renal lesions producing pyuria are chronic diffuse inflammation, tuberculosis, renal abscess, pyonephrosis, pyelonephritis, and cancer.

When the pyuria is of vesical origin, the urine is often ammoniacal when voided, and, owing to accompanying mucus, the urine is more tenacious than that of renal pyuria. Triple-phosphate crystals and bladder epithelium are almost always present, the former often in great abundance. Cystitis of every form, whether due to stone, neoplasm, retention, or tuberculosis, is a common cause of the condition.

If the urine contain long threads of pus, the disease is probably located in the prostate. Pus from the urethra is usually easily recognized, and may be determined by examination of the urethra or the discovery of gonococci.

The best means of determining the quantity of pus discharged in the urine is by the use of the centrifuge, which shows the exact percentage of pus present. A fairly close estimate may be made by counting the number of corpuscles. The number of pus cells varies, according to Hottinger (*Zeitschrift für die medicinischen Wissenschaften*, No. 15, 1893), from 1,400 in a cubic centimetre of urine from a mild case of cystitis to 150,000 in that from a severe vesical catarrh resulting from cancer. When exceeding 40,000 per cubic centimetre the urine should be diluted with a three-per-cent. salt solution, an acid reaction being retained to prevent disintegration of the cells. As already stated, the number of pus cells discharged in a day may far exceed the probable number of leucocytes present in the entire blood circulation of the individual. Goldberg (*loc. cit.*, No. 36) makes an important addition to the method of Hottinger, by which it is possible to detect an albuminuria of renal origin notwithstanding the presence of pus. He found that the presence of 100,000 pus cells in a cubic centimetre of urine produced one per cent. of albumin. If, therefore, the percentage of albumin be one per cent. or greater in the presence of 50,000 pus cells to a cubic centimetre, the albuminuria cannot be altogether the result of the suppuration.

Blood.

Blood corpuscles may find their way into the urine from any part of the urinary passages, or may be accidentally present, as during menstruation. When abundant they give more or less characteristic appearances to the urine, the color varying from a dark-red or smoky hue in acid urine to a bright red in that which is alkaline; or there may be a reddish-brown granular sediment. Coagula are found especially when the hemorrhage has occurred in the ureter or urethra, sometimes when in the bladder. Chemical tests always reveal albumin. The corpuscles, usually scattered singly over the field of the microscope in renal hemorrhage, rarely in rouleaux, exhibit the characteristic appearance of yellowish biconcave discs, with an occasional leucocyte not easily distinguished from other spherical bodies (Fig. 59). Their form is best preserved in acid urine, and as the speci-

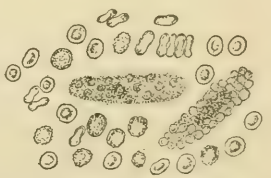

Fig. 59.—Blood Cells and Blood Casts.

men becomes old their edges become dentated. This appearance is more pronounced in concentrated urine. In urine of low density, on the other hand, they often swell and become biconvex or spherical in form, at the same time losing their color.

One of the most reliable methods of determining the quantity of blood present in the urine is by the use of the centrifuge. From the ratio of blood to urine the entire quantity lost in twenty-four hours may be calculated. If, however, more than two minutes be consumed in centrifugal sedimentation, some of the blood corpuscles will be destroyed.

Goldberg has applied the method of Hottinger to the estimation of the quantity of blood in the urine, counting the number of corpuscles. The count must be made immediately after the urine has been voided to obtain accurate results. The estimation of the percentage of blood is comparatively easy. If, for example, 1 c.c. of urine is found to contain 50,000 blood discs, it is evident that one per cent. of blood is present, since the normal number of corpuscles in 1 c.c. of blood is 5,000,000. Each 100 c.c. of the urine would therefore contain 1 c.c. of blood, providing that the blood of the individual be normal. Goldberg extends his method further to the determination of albuminuria of renal origin in the presence of blood from another source.

Clinical Significance.—The clinical significance of hæmaturia necessarily depends upon the source of the blood; this must therefore be

Fig. 60.—Peculiar Forms of Blood Corpuscles Found in Hæmaturia of Renal Origin. (Gumprecht.)

first determined. Renal calculi, wherever located, sooner or later, as a rule, induce the presence of blood in the urine, most frequently soon after exercise, pus cells generally being present at the same time. Other causes of hæmaturia are renal abscess, embolism, hydatids, traumatism, acute infections, purpura hæmorrhagica, phlebitis of the crural or uterine veins, and the ingestion of such drugs as turpentine or cantharides in large doses.

The kidney is almost certainly the source of the blood if the urine be of low specific gravity, acid in reaction, of a homogeneous, brownish or smoky color, and if it contain, in addition to blood, renal casts and renal epithelium. The discovery of blood casts renders this conclusion positive. Gumprecht has found that in renal hæmaturia the red blood discs are less numerous than in that of

vesical origin and that they almost invariably undergo fragmentation as a result of the action of urea. They often assume swollen and peculiar forms also (Fig. 60), while in vesical hæmaturia these cells show no alteration beyond crenation.

In the acute forms of nephritis blood, although generally present, is found in only small quantity and only until the subsidence of the more acute manifestations of the disease. Hæmaturia almost never occurs in chronic diffuse nephritis, but is comparatively frequent and exceedingly persistent in malignant and cystic diseases of the kidney. It sometimes occurs in amyloid disease and in syphilitic granuloma. Hemorrhage due to tuberculous disease of the kidney, by no means infrequent, is usually intermittent in occurrence, and the urine contains pus, tissue *débris*, and tubercle bacilli. Profuse hæmaturia has recently been observed as an initial symptom of tuberculous nephritis. Finally, a certain number of cases must be attributed to a hemorrhagic diathesis.

Urinary Casts.

Renal or tube casts are small, translucent, cylindrical bodies, of variable length, varying in width from one-thousandth to one-five-

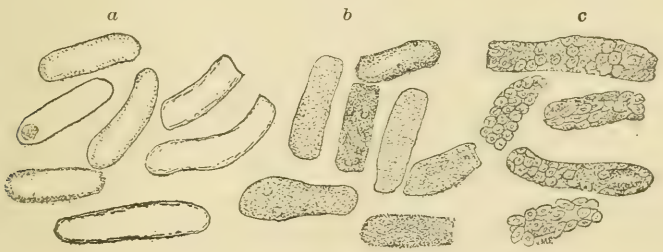

Fig. 61.—Renal Casts. *a*, Hyaline; *b*, granular; *c*, epithelial.

hundredth of an inch, rarely larger; straight, curved, or twisted in form, and often found in the urine. There are three views in regard to their nature. In the first place, they are looked upon as moulds of the renal tubules, caused by the packing of the *débris* of disintegrated epithelium, blood, etc., into the tubules under the pressure of the urine, which finally forces the cast out into the collecting tubule and on through the lower passages. The second view is that the casts are a product of the secretion of the epithelial cells of the tubules, under the stimulus of inflammatory irritation or as a result of faulty metamorphosis. The third and more tenable theory is that casts are a product of certain coagulable elements of the blood, which gain access to the uriniferous tubules through pathological lesions of the tubules or of the blood-vessels, the various crystals and products of epithelial

disintegration or desquamation which are often presen being simply entangled in this material as it coagulates. Of the nature of this coagulable substance we know but little. It is evidently closely allied to the proteids, although it is not identical with any that have been isolated. Albumin is very rarely if ever absent from urine containing true renal casts. Three principal varieties of casts are recognized (Fig. 61):

1. Hyaline casts, clear, homogeneous, or very finely granular in appearance, often so delicate in outline as to be recognized with some difficulty under the microscope.

2. Casts consisting largely of anatomical elements, epithelium, blood, pus, bacteria, and known as epithelial casts, blood casts, etc.

3. Granular casts, consisting largely of the products of the disintegration of such anatomical elements as epithelium and blood, and including all casts having a distinctly granular appearance. The fatty cast is usually assigned to this class.

Hyaline Casts.—These are exceedingly pale, almost perfectly translucent, homogeneous or very finely granular cylinders, often difficult of detection unless their presence is revealed by attached epithelium or other adherent matter. Their nature and origin remain alike obscure, but they are probably derived from the coagulable elements of the blood already referred to, and they possibly form the basis or matrix of most other kinds of casts. The experiments and investigations of Ribbert tend to prove that they consist of serumalbumin, which, after being exuded into the tubules, has undergone coagulation, under the influence of certain chemical conditions. The facts that they are probably never found in the absence of albumin and that they are soluble in acetic acid, both lend support to this theory. Hyaline casts may be long and slender, or shorter and broad, their shape depending, no doubt, upon that of the tubules in which they are formed. The long cylinders are supposed to come from the small tubules of the kidney, the broad casts from the straight or collecting tubules.

The *waxy cast* closely resembles the hyaline, but differs from it to some extent in appearance and chemical reaction, being more highly refracting, often cloudy, rather longer and broader, and being marked by indentations or constrictions along its margins, and not being soluble in acetic acid. Sometimes it yields the reaction of amyloid degeneration when treated with compound iodine solution or with methyl violet, a reaction which does not, however, signify the existence of amyloid disease of the kidneys (Fig. 62, *a*).

Granular Casts.—These casts also vary in size, shape, and color, as well as in the fineness of their granular matter, and often appear

in fragmentary condition, as may be recognized by the broken appearance of their extremities. White, yellow, gray, and brown are the most frequent colors. Epithelium, blood, leucocytes, fat globules or crystals may be found adhering to their surface (Fig. 61, *b*).

Fatty Casts.—This name is given to casts which are made up chiefly of oil globules or fat crystals, both forms of fat being sometimes present in the same cast (Fig. 62, *b*).

Epithelial Casts.—These are usually easily recognized. They may

FIG. 62.—Renal Casts. *a*, Waxy; *b*, fatty; *c*, amorphous urate and other false casts.

have the appearance of being made up entirely of epithelial cells, or they may have a homogeneous, hyaline, interior part or core, to which the epithelial cells adhere. Another form (pseudocasts) is occasionally met with, which appears to consist of the epithelial lining of a portion of a tubule which has become detached without separation of the individual cells. In appearance the epithelial cells may be fairly normal, or they may show various degrees of degeneration, indicated by the presence in them of finely granular or molecular fat.

Blood casts are usually short, uniform in diameter, with rounded ends. They are of comparatively infrequent occurrence, and are found without difficulty, except in the presence of a large number of free blood cells.

Pus Casts.—Casts made up entirely of pus are rarely seen. Ordinarily a few pus cells are found adhering to the surface of the granular or epithelial casts.

Bacterial Casts.—Casts composed largely of micrococci are occasionally met with. Under moderate magnification they closely resemble the granular casts, although they are usually more opaque; but with a high power of the microscope they can readily be distinguished. Another distinguishing feature is the fact that they resist the action of strong mineral acids and caustic alkalies.

Clinical Significance.—The presence of renal casts is always indicative of a pathological condition, the gravity of which is to be estimated in part by the character of the casts present, but to a greater

extent by the character of accompanying conditions. Their presence in albuminuria denotes the renal origin of the albumin, and adds to the gravity of the latter symptom, unless only a few hyaline casts be present without the accompaniment of other morphological elements than a few normal epithelial cells. The association of granular casts, fatty casts, or free or attached fatty degenerated epithelium always denotes the existence of a nephritis, usually chronic in character. In the presence of more than a trace of albumin, hyaline casts alone signify a disturbance of renal blood pressure, congestion, or an acute nephritis.

The presence of epithelial casts in the urine denotes an inflammatory condition of the region from which they are derived. If this inflammation be of chronic form, the epithelium, as a rule, shows a fatty change; fatty and granular casts may also be present.

The significance of blood casts is the same as that of hæmaturia. While they do not afford positive evidence of organic renal disease, they frequently depend upon an acute productive nephritis, especially that of scarlatina, and they are the most positive evidence that a hæmaturia is of renal origin. Casts containing melanin may occur in melanuria, with degenerative changes in the kidney, or as a result of melanotic neoplasms. Pus casts denote suppurative disease of the kidney.

Granular casts, as a rule, denote a chronic disease of the kidneys, such as advanced diffuse nephritis. Riedel considers the occurrence of brown casts pathognomonic of fracture.

Bacterial casts denote a septic inflammation of the kidneys, often that resulting from an infarction or an ascending pyelonephritis.

The waxy cast may occur in any form of renal disease, and is never pathognomonic of amyloid disease, as was once supposed.

False Casts or Cylindroids.—Various bodies, more or less closely resembling renal casts, have been described under various names. They are supposed by different authors to consist of coagulated mucus, or of the secretion of glands along the urinary tract or the seminal tubules. They are probably due in most instances to the presence of local inflammatory processes, short of organic lesions in the kidney or lower urinary passages. They often occur without albuminuria. They are usually seen in the form of long, flat, wavy, or tortuous bands, often branching, colorless, and seldom showing adhering cells. They are not regarded as of serious import. Mention should also be made of the cast-like bodies composed of amorphous urates, which Leube asserts may be obtained from any urine by condensing it *in vacuo* at a temperature between 37° and 39° C.

Method of Examining for Casts.

The failure to find casts in albuminous urine is very often a result of faulty sedimentation or of too long delayed examination. It is here that the centrifuge is of greatest service, since it enables us to make a microscopic examination immediately, before the casts have been attacked by bacteria or affected by the development of alkalinity.

A drop of the urinary sediment is placed on a glass slip and examined without a cover, or it may be placed in a shallow cell and the cover-glass placed over it. The cells of slips prepared for the hanging drop are too deep for examination with a high power, and a piece of a hair placed under each side of the cover will answer the purpose of the cell. A moderately low power should first be used to determine whether casts are present; then a high power to determine their nature. The slip and cover-glass must be strictly clean, and all excess of fluid should be removed from the edges of the cover with a piece of blotting paper. The light should not be too bright, and may often be used to advantage when thrown from a point a little to one side, so that it passes obliquely through the specimen, even though only a portion of the field be illuminated. The hyaline cast in particular requires this method of illumination. By turning the fine adjustment screw back and forth over a small part of a revolution, the outline of objects is more easily recognized. The exact form of a body may sometimes be determined by carefully touching the cover-glass with a needle, thus causing the body to move or roll over. It is rarely necessary or advantageous to resort to the use of the staining processes recommended by some writers; but the presence of a little bile pigment in the urine frequently renders accompanying casts beautifully brilliant and distinct.

If a stain is desired, all that is usually necessary is the addition of a drop of a weak solution of one of the aniline dyes to the sediment. Grosz, of Vienna, has obtained the best results from the use of alizarin. To a drop of the sediment on a slip a drop of a one-per-cent. solution of sodium alizarin sulphonate is added. Elements of acid reaction appear yellow; those of alkaline reaction, violet; those of neutral or of only feebly acid reaction, red. Renal casts stain yellow, and, according to Grosz, may be thus distinguished from mucin cylindroids, which appear red. The same variation of color is brought out in epithelial cells in urine of different reactions.

SPERMATOZOA.

Spermatozoa are little thread-like bodies, about one-six-hundredth of an inch long, with flattened, oval heads. Under favorable condi-

tions of warmth and moisture they exhibit a vermicular motion for many hours, but are usually devoid of motion when found in urinary sediments. Strong acids, alkalies, alcohol, and water have the power to destroy their motion. They dissolve in boiling potassium-hydroxide solution, but not in sulphuric, acetic, or nitric acid, or in hot sodium solution. When very abundant the seminal fluid causes slight turbidity of the urine, or a whitish sediment giving a strong reaction of phosphates.

Significance.—The presence of spermatozoa in the urine denotes contamination with spermatic fluid. Their discovery in the urine of a woman may have medico-legal value. They are always found in the discharge of true spermatorrhœa; they sometimes occur as a result of the compression of the seminal ducts by the passage of hardened fæces from the rectum, and cases have been reported of their presence in the urine as a result of stricture with urethral dilatation above the stricture. Injury or disease of the spine, anæsthesia, and epileptic seizures are often followed by the appearance of spermatozoa in the urine. (Many of the subjects considered in this section will be found more fully treated in the chapter on Diseases of the Urine, Vol. I., p. 527.)

Fragments of Tumors.

The urine sometimes contains fragments or disintegrated matter from tumors of the bladder; rarely from those of the kidney. Fragments of carcinomata and of papillomata have been thus recognized. Unfortunately, however, these fragments are usually too small, or they are in too advanced a state of degeneration to permit an accurate determination of their character; and positive diagnosis from mere fragments is never justifiable, owing to the fact that the surface layer of a neoplasm is not always of the same type as the tumor proper. Senn's remark that "The greatest blunders in diagnosis and treatment have been committed by surgeons of eminence through placing too great reliance on the microscopic examination of fragments of tumor tissue" is applicable here.

Fragments of the villous papilloma may sometimes be voided with the urine, or may be torn away with the catheter. This growth is formed of branching papillæ covered with transitional epithelium, the superficial layers of which may have been removed by maceration and friction within the bladder, so that only its gross appearance can generally be made out from fragments found in the urine.

Crystals of hæmatoidin are sometimes found in the necrotic fragments and, according to von Jaksch, are pathognomonic of carcinoma.

They are small rhomboidal, yellowish or brownish-yellow crystals, occurring in little tufts. When treated with nitric acid under the microscope they exhibit the play of colors which is characteristic of biliary coloring matters.

Animal Parasites.

Distoma Hæmatobium.—The changes which occur in the urine as a result of the ravages of this parasite are due for the most part to a constriction of the small submucous blood-vessels of the bladder and the subsequent escape of the parasite's eggs through ulceration of the overlying tissue. As a result of this ulceration, blood, pus, and sometimes fat are also found in the urine. For a complete description of the parasite, the reader is referred to Vol. VIII., p. 580. The eggs are oval, about one-two-hundredth inch long, with a sharp projecting anterior extremity and containing a distinctly visible embryo. The masses of ova which are discharged into the bladder sometimes become the nuclei of calculous formations.

Filaria Sanguinis Hominis.—The natural history of this parasite, the diseases which it produces, their symptomatology, etc., are considered in Vol. VIII. of this work. Its interest here lies in the fact that filariæ are often found in comparatively large numbers in chylous urine. The parasite is about as wide as a red blood corpuscle and about fifty times as long. It has a short, rounded head and a long, pointed tail. The body appears granular, with transverse striations.

Echinococcus.—It is very rarely that the hooklets and scolices of the echinococcus cyst find their way into the urine, for it is only by a rupture of a cyst into some part of the urinary passages that they are given this avenue of escape from the body. When this occurs, microscopic examination of the urinary sediment may reveal the characteristic hooklets, scolices, or fragments of them and pieces of the chitinous membrane, usually with more or less blood, pus, and cellular *débris.*

Trichomonas.—A few instances only are on record in which this parasite was discovered in the urine. It is probable that more than one species has been observed, since the descriptions do not entirely agree. Dr. George Dock describes the parasite as observed by him (*Medical News*, December 12th, 1894) as an oval, ovoid, or irregular body from 0.015 to 0.020 mm. long and from 0.008 to 0.015 mm. wide, having from two to four flagella at one end and sometimes a flagellum-like tail at the other. At one side, running back from the base of the flagellum is an undulating membrane, not always visible. The structure of the body is granular, sometimes homogeneous. An oval

nucleus with a long narrow chromatin body was present, sometimes also vacuoles, but there was no evidence of a mouth or of internal structure.

Among other parasites occasionally found in the urine mention may be made of the Oxyuris vermicularis and the Strongylus gigas. A peculiar *amœba* has also been described by Baelz and an *infusorium* by Hassal.

Vegetable Parasites.

Normal urine is seldom free from bacteria when voided, and after it has been allowed to stand for some time at ordinary temperature it becomes densely populated by micro-organisms, which find in it an excellent culture medium. Recent investigations have shown that the urethra is constantly the abode of numerous, for the most part harmless, microbes, some of which are almost invariably carried off by the urine. The bladder has also been found to contain many bacteria, some innocent, others pathogenic or capable of becoming pathogenic under favorable circumstances. But, on the other hand, comparatively few of the reported observations have been made upon individuals who had never been the subjects of genito-urinary disease, catheterization, or other influences capable of conveying bacteria into the bladder, and consequently it is difficult to place a proper estimate upon the observations. There can be no doubt that the urine is an avenue for the elimination of micro-organisms which gain entrance into the circulation. Ultzmann has found bacteria in the urine of persons who live in unhealthy, malarial, marshy regions, in bad atmospheres, and in those who spend much time in dissecting rooms or morgues, and, according to Beidl and Kraus, microbes injected into a vein appear in the urine within from five to twenty minutes, the urine remaining clear and free from albumin.

Abnormal urine is rarely, though sometimes, free from bacteria when voided. Nearly forty varieties of micro-organisms have been recognized in the urine. These belong to two distinct classes, namely, to the pathogenic and the non-pathogenic.

Non-Pathogenic Bacteria.

These embrace all those bacteria which are not capable of producing disease and may be made to include moulds, the yeast plant, and the fission fungi.

Moulds seldom form upon urine, even after long standing, unless sugar is present. After diabetic urine has undergone alcoholic fermentation, however, a luxuriant growth of mould frequently forms on its surface, along with great numbers of the yeast plant. Sarcinæ

have been found in acid urine. They are somewhat larger than those of the stomach and quickly disappear under the influence of alkaline fermentation.

The *yeast plant* is found in the urine in the form of single cells or in the form of branching plants, many of the cells having one or more small buds. The individual segments are of oval shape, of variable size, averaging about that of a leucocyte, the larger cells containing nuclei. They grow only in acid urine and in the presence of sugar.

The so-called *fission fungi* belong for the most part to the class known as saprophytic bacteria, whose office it is to break up dead

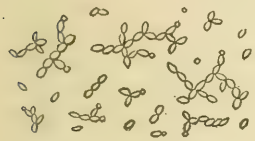

FIG. 63.—Yeast Plant.

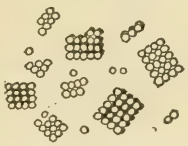

FIG. 64.—Sarcinæ of Urine.

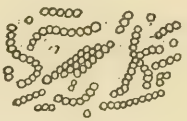

FIG. 65.—The Micrococcus Ureæ.

organic tissues into simpler forms of matter. Upon their action depends the ammoniacal decomposition of urine in which urea becomes converted into ammonium carbonate. It was once supposed that this decomposition depended solely upon the action of a micro-organism known as the micrococcus ureæ, but more recent investigation has shown that nearly all bacteria found in the urine have this power.

The *bacterium ureæ* is a rather large micrococcus growing usually in chains, sometimes singly and in great numbers (Fig. 65). These bacteria are found only in slightly alkaline urine which is entering upon or undergoing putrefactive change. Such urine is generally voided by persons who are subject to more or less complete retention to urine, owing to urethral stricture, cystitis, paraplegia, enlarged prostate, etc. The urine, as is always the case when a large number of bacteria is present, is cloudy, even opaque, and shows an undulatory or eddying motion when shaken. It has a "stale" odor, which is sometimes extremely penetrating and offensive.

Pathogenic Bacteria.

The pathogenic bacteria, micro-organisms which are capable of producing disease, may be described under two heads, namely, micrococci and bacilli.

The micrococci found in urine belong for the most part to the class known as pus-formers, or bacteria which produce suppuration, and include the staphylococcus pyogenes albus, aureus, and citreus; the streptococcus ureæ, pyogenes, and rugosus; several diplococci,

and many others. To this class belongs also the gonococcus of Neisser.

The most important of the bacilli found in the urine are the bacillus coli communis, the bacillus typhosus, and the bacillus tuberculosis, besides which several have been reported. From the occurrence of these bacilli in the urine as a result of experiments on lower animals it is believed that these micro-organisms are at least in part eliminated from the system through the kidneys, either during or after the prevalence of the diseases to which they belong.

The micrococci as a rule require no special methods of staining to bring them into view, all that is necessary being to place a drop of

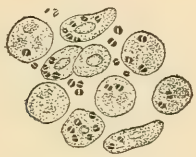

Fig. 66.—Gonococci.

Fig. 67.—Bacilli Tuberculosis.

the urinary sediment on a glass slip, add a drop of a solution of any aniline stain, wash off the excess of coloring matter after a few minutes, and examine with a high power of the microscope.

The Gonococcus.—This organism differs in some respects from the other micrococci and requires further description. It has a hemispherical shape and is so arranged in pairs that the inner, flat, or slightly concave side of each hemisphere is separated from that of its fellow by only a narrow interval (Fig. 66). Sometimes the cocci are arranged in groups of fours, like tetrads. Each coccus is small, devoid of flagella and spores, and motionless. It is most readily stained by weak solutions of aniline blue or violet. The gonococcus is usually found in pus cells or attached to epithelium. While it is recognized as the cause of gonorrhœa, it should be remembered that urethritis is sometimes produced by the bacillus coli communis or the staphylococcus pyogenes.

Bacillus Tuberculosis.—Tubercle bacilli are sometimes found in the urine in great numbers, especially in purulent urine, aggregated into colonies which sometimes assume an S-shape; but they may be so few as to render their detection extremely difficult (Fig. 67). The method of search for them is the same as that employed in examination of sputum, but is rendered much more difficult by the greater dilution of the fluid and the low specific gravity of the bacillus, which renders sedimentation difficult even with the centrifuge. The urine should be obtained for examination by catheterization, in order to

avoid contamination by the smegma bacillus, which possesses the same form and staining properties as the bacillus tuberculosis.

Method of Staining.—Ziehl's carbol-fuchsin staining fluid has generally proved most satisfactory. The formula for this stain is: Fuchsin, 1 part; alcohol, 10 parts; five-per-cent. solution of carbolic acid, 100 parts. The process may be thus described: After obtaining a good sedimentation, a drop is removed with a pipette and placed on a cover-glass. This is dried with moderate heat and then passed three times through the flame. A drop of carbol-fuchsin solution is then spread upon the entire surface of the dried sediment and the glass is held at some distance above the flame until a white vapor begins to rise. It is then kept at this temperature for from three to five minutes by moving it back and forth over the flame. If the fluid evaporates from the edges of the glass, it is replaced by fresh fluid. The specimen is then washed with water, the excess of water is removed with paper, and a drop of twenty-five per cent. sulphuric acid or of thirty-three per cent. nitric acid is dropped upon it and left for exactly thirty seconds. The acid is then washed off with water, the specimen is dried and mounted in balsam. A counter stain may be used if desired. Gabbett's stain, consisting of methyl blue 2 parts, sulphuric acid 25 parts, water 75 parts, applied for thirty seconds, after the Ziehl stain is one of the best.

The bacillus tuberculosis is a rod-shaped body from 1.5 to 3.5 μ long and a third as wide, often slightly curved and having rounded ends.

Bacillus Typhosus.—This is a rod-shaped bacillus, very variable in length and breadth, but usually from 2 to 4 μ long and a fourth as broad. It has flagella and is endowed with motion, but is usually motionless when found in the urine. It may be stained by Ziehl's method, acetic acid being used as a bleach instead of sulphuric or nitric acid; but it so readily parts with its stain that better results are obtained from allowing it to be acted upon for twenty-four hours by Löffler's alkaline methylene-blue solution (saturated alcoholic solution of methylene blue, 30 parts; 1:10,000 aqueous solution of potassium hydroxide, 100 parts). After staining, the specimen is washed, quickly dehydrated with alcohol, cleared with xylol, and mounted in balsam.

Bacillus Coli Communis.—This bacillus is of interest chiefly because of its being the most frequently present of all pathogenic bacteria which invade the urinary organs, often standing in etiological relation to urethritis, cystitis, pyelonephritis, and other suppurative diseases of the urinary tract. Morphologically it bears so close a resemblance to the typhoid bacillus that special methods of differen-

tiation are required, for a full description of which the reader is referred to the works on bacteriology.

Ptomains, Leucomains, Toxins in the Urine.

All micro-organisms are believed to have the power to produce definite chemical substances as a result of their vital activity. These substances are numerous and varied; they vary not only with the different species of bacteria, but also with the medium which composes their food. Some of these products are acids, some alkalies, others bases. The term *ptomain* was at first applied to the basic organic chemical compounds (diamins) formed in the process of putrefaction of dead organic matter. Now, however, it is applied to all "organic chemical compounds, basic in character, formed by the action of bacteria upon nitrogenous matter" (Vaughan and Novy). Some of these compounds are poisonous, others are not. The name toxin was given by Brieger to the poisonous ptomains, but it has since been applied to many poisonous products of bacterial action which are neither basic nor proteid in character, and whose nature is but little understood.

Leucomains, on the other hand, are basic substances which result from tissue metabolism within the body, resulting either from fermentation which is not dependent upon the action of bacteria, or from retrograde metamorphosis. They are the alkaloidal products of physiological processes. While ptomains are formed largely in the intestinal canal, leucomains have their origin for the most part in the tissues.

Ptomains are intermediate or transitional states of matter in the process of the reduction of organic compounds into simpler organic matter. Kossel has shown that at least some leucomains "are antecedents of end products of metabolism." Ptomains may be developed within the body, or they may be admitted with food or drink; the gaseous products of bacterial activity may also gain access to the body.

All ptomains contain nitrogen, thus resembling the vegetable alkaloids—those containing oxygen further resembling the fixed alkaloids, those devoid of oxygen resembling the volatile alkaloids.

To Selmi is due the credit of having first called attention to the probable formation of basic substances in the living body during the existence of pathological conditions brought on by the entrance of pathogenic bacteria and to the fact that infectious diseases are accompanied or followed by the elimination of more or less characteristic products; and to the detection of these in the urine he attached

great diagnostic importance. Although his announcement was made in 1880, and although a vast number of investigations have since been made, comparatively few of the many chemical substances known to belong to this class, and believed to be eliminated with the urine, have yet been isolated. Their importance to pathology, particularly to that of the kidneys, is becoming more and more generally recognized. Sternberg expresses the belief that in those forms of nephritis which are known under the general name of Bright's disease, "the primary cause of the renal inflammation is, as a rule, perhaps always, some toxic substance in the blood which acts as an irritant to some portion of the renal parenchyma."

We have an example of the presence of leucomains in normal urine in perhaps all of the basic substances included in the uric-acid group, since these are products of tissue metabolism. Ptomains are probably always an abnormal constituent of the urine, for they do not result from normal metabolism. The principal ptomains which have been isolated from the urine are cadaverin, putrescin, trimethylamin, and beatin; but none of them, so far as is known, is of clinical significance.

It would be out of place in a work of this character to describe the methods employed for the extraction of these substances, for much space would be required, and the difficulties encountered and the liabilities to err at almost every step in the processes are such as to render them useless outside of the chemical laboratory.

The methods generally employed for the extraction of ptomains are the Stas-Otto method or one of its modifications, the Dragendorff method, and the Brieger method, the last of which is best adapted to urinary analysis.

Cadaverin ($C_5H_{14}N_2$) is a rather thick, water-clear fluid of offensive odor, resembling coniine or semen. It fumes in the air, from which it absorbs carbonic acid and finally crystallizes as a carbonate. It is a constant ingredient of the urine of cystinuria. As it is never found in cultures in which some form of the vibrio is not present, its presence in decomposing urine is attributed to the action of this organism. Verigo considers it a normal product of pancreatic digestion. Its origin in cystinuria is attributed by some to the intestinal canal, but it has not been found simultaneously in the stools. It is also a constant product of the cholera bacillus, regardless of the culture medium, but it has not been isolated from the urine of cholera patients; some authors therefore refer the symptoms of cholera to its retention.

Putrescin ($C_5H_{12}N_2$) is a water-clear, rather thin liquid, which fumes in the air and emits an offensive odor closely resembling that of

cadaverin. From the air it also absorbs carbonic acid. It is almost always associated with cadaverin, appearing, as a rule, a little later. It is therefore found in the urine of cystinuria, in old cultures of the comma bacillus, but not in the urine of cholera patients.

Trimethylamin (C_3H_9N) in its basic state is a strongly alkaline liquid freely soluble in water and possessing a fishlike odor. It has been found in the cultures of quite a number of bacteria, including the streptococcus pyogenes, the proteus vulgaris, and the comma bacillus, but its significance has not been determined. Stadthagen found it in normal urine.

Beatin ($C_5H_{13}NO_3$) is best known from its occurrence in the vegetable kingdom. It was found in the urine by Liebreich. It is of no known significance.

The leucomains are divided into two well-defined groups, the uric-acid group and the creatinin group, from their relation to uric acid and creatinin.

It would not be expedient in the present state of our knowledge to enter into a description of the numerous leucomains which have been found in the urine and the methods that have been employed by various investigators for their isolation, and the same may be said of the toxins which do not belong to either of the classes already considered. As Vaughan and Novy aptly remark: "It is comparatively easy (from the result of the application of the so-called alkaloidal tests) to report upon the presence of alkaloids in so complex a fluid as the urine. It is much more difficult, however, to isolate such bodies in a chemically pure condition, satisfying the requirements of exact research."

The more important of the leucomains that have been isolated belong to the uric-acid group. They are, in isomeric order, adenin, hypoxanthin, xanthin, heteroxanthin, methylxanthin, paraxanthin, carnin (or a substance closely resembling carnin), and episarkin. Some of these bases are normally present in the urine, others have been found only in diseased conditions or after the administration of medicines. Their pathological importance generally depends upon their retention, rather than upon increased elimination in the urine. This is true particularly of paraxanthin, the most poisonous of the group, and the only one to which consideration will be given in this place.

Tests for Paraxanthin.—1. To a few drops of thick, concentrated urine, add a few drops of concentrated solution of potassium hydroxide. If much paraxanthin be present, a white, glittering precipitate is formed; if but little be present, the fluid becomes slightly turbid, the turbidity increasing after standing.

2. A little chlorine water containing a trace of nitric acid is added to the urine and the mixture is evaporated to dryness. The residue is then exposed to the fumes of ammonia, and a rose-red color is produced if paraxanthin be present.

Clinical Significance.—Of the xanthin group, paraxanthin is the most toxic, xanthin ranking next. Although the investigations of Salomon and others have demonstrated their poisonous effects on small animals, comparatively little has been developed in regard to their action on man. Rachford, of Cincinnati, has shown, in a series of articles read before the Association of American Physicians (*Medical News*, May 26th, 1894; November 3d, 1894; September 7th, 1895, and May 16th, 1896), that paraxanthin occurs in increased quantity in the urine during or immediately after attacks to which he applies the names leucomain headache, leucomain epilepsy, leucomain gastric neurosis, and leucomain asthma, and in some cases of lead encephalopathy.

The Toxicity of the Urine.

The urine, whether normal or pathological, is in a high degree poisonous to the human organism as well as to the lower animals. The cause of this toxicity lies in the presence of its chemical constituents, the removal of which from the blood it is doubtless the chief office of the kidneys to perform. Of the many investigations which have been made on this subject, those of Bouchard are the most valuable. He attributes the greatest part of the toxicity of normal urine to the coloring matters. He describes, however, seven kinds of poisons which he has found in the urine, including urea and potassium compounds. These bodies, acting alone, produce respectively diuresis, narcosis, salivation, convulsions (produced by two bodies), contraction of pupils, and reduction of heat.

To Bouchard we are indebted also for a method of expressing the comparative degrees of toxicity of different specimens of urine. The unit of comparison, or toxic unit, is the quantity of a given specimen of urine which is required to kill a rabbit weighing 1 kgm., or as it is usually expressed, 1 kgm. of animal. To determine this quantity, the urine is slowly injected into the posterior vein of a rabbit's ear until death occurs, then calculating from the quantity required and the weight of the animal. In making comparisons with this unit, it is necessary to establish a urotoxic coefficient, which Bouchard defines as the quantity of toxic matter which a unit of weight produces in a unit of time. The urotoxic coefficient of a person is the number of toxic units formed in twenty-four hours by a kilogram of that individual. If, to use his example, it is supposed that a healthy man

of 60 kgm. weight excretes 1,200 c.c. of urine, 50 c.c. of which are capable of killing 1 kgm. of animal, then the total 1,200 c.c. would kill 24 kgm. of animal; each kilogram of the man forms in twenty-four hours what would kill 400 gm. of animal, and his urotoxic coefficient is 0.4. The average normal coefficient is, according to Bouchard, 0.464.

The urotoxic coefficient has been found to vary over a wide range under the influence of diet, exercise, and rest, and in the presence of various abnormal conditions, including nearly all the infections, many functional and organic diseases, and neoplasms.

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